CONTENTS OF VOLUME V

January

Surgical Treatment of Angina	*William Dock*	1
Thromboendarterectomy for Coronary Artery Disease	*Charles P. Bailey*, *Dryden P. Morse*, *William M. Lemmon*	3
Rupture of the Heart in Myocardial Infarction. Clinical and Pathologic Observations	*Louis H. Sigler*	14
Disturbances of Rate, Rhythm and Conduction in Acute Myocardial Infarction. A Statistical Study of 153 Cases	*Elias S. Imperial*, *Rodolfo Carballo*, *Henry A. Zimmerman*	24
Thumping of the Precordium in Ventricular Standstill	*David Scherf*, *Carl Bornemann*	30
Incidence of Myocardial Infarction Correlated with Venous and Pulmonary Thrombosis and Embolism	*Wilbur A. Thomas*, *Jack N. P. Davies*, *Robert M. O'Neal*, *Amador A. Dimakulangan*	41
Coronary Heart Disease in the South African Bantu	*W. Laurie*, *J. D. Woods*, *G. Roach*	48
Problem of Heart Disease in India	*K. S. Mathur*	60
A Pharmacodynamic Approach to the Evaluation of Nitrites in the Treatment of Angina Pectoris	*Irving Hirshleifer*	66
Plethysmographic Studies in Atherosclerosis Obliterans	*Alfredo Buzzi*	72
Ventricular Fibrillation During and After Coronary Artery Occlusion. Incidence and Protection Afforded by Various Drugs	*Sam E. Stephenson, Jr.*, *Thomas F. Parrish*, *Ira T. Johnson, Jr.*, *James S. Anderson, Jr.*, *James E. McCarty*, *John R. Wilson*, *Clifton K. Meador*, *George R. Meneely*, *Richard K. Cole*, *Frank M. Bauer, Jr.*, *Morse Kochtitzky*, *Lester L. Hibbitt*, *Edwin R. Young*, *Henry N. Meiers*, *Con O. T. Ball*	77
Recovery of Peripherally Injected Materials from the Heart at Varying Intervals after Death	*Ira N. Rosenstein*, *Fred Wasserman*	88
The History of Coronary Sclerosis	*Paul Klemperer*	94
Comparison of Laxative Action of Bisacodyl Suppositories and Glycerin Suppositories in Acute Myocardial Infarction	*Jules Levine*, *Seymour H. Rinzler*	108
Relative vs. Organic Mitral Insufficiency	*A. A. Luisada*, *J. Szatkowski*	111
Precipitation of Myocardial Infarction by Postural Hypotension	*Fritz Mainzer*	113
Localized Pulmonary Fluid Collections in Congestive Failure Simulating Tumors. Phantom Tumors of the Lung	*Isidore Stein*, *Joseph Weinstein*	117
Extreme Hypertrophy of the Left Atrial Appendage. The Case of the Giant Dog Ear	*Edmunds Grey Dimond*, *C. Frederick Kittle*, *Douglas W. Voth*	122

Primary Mesothelioma of the Pericardium	*Jean L. Forest* *Michael C. Kozonis*	126
Progress Notes in Cardiology		130
Book Reviews		132
College News		133
Announcements		134

February

Introduction to Symposium on Ventricular Septal Defects	*Milton S. Saslaw*	135
Anatomy, Physiology and Natural History of Simple Ventricular Septal Defects	*J. Francis Dammann, Jr.* *W. M. Thompson, Jr.* *Omar Sosa* *Ignacio Christlieb*	136
Some Physiologic and Hemodynamic Observations in Ventricular Septal Defect	*Otto García* *Heriberto Mercado* *Alberto H. Cañero* *Agustin Castellanos* *Frank Barrera* *with the technical assistance of* *Francisco Zerquera*	167
Isolated Ventricular Septal Defects. An Anatomic-Hemodynamic Correlation	*Elias S. Imperial* *Cid Nogueira* *Earle B. Kay* *Henry A. Zimmerman*	176
Clinical Findings in Ventricular Septal Defects	*L. George Veasy*	185
The Auscultatory and Phonocardiographic Signs of Ventricular Septal Defects	*Selvyn Bleifer* *Ephraim Donoso* *Arthur Grishman*	191
The Electrocardiogram and Vectorcardiogram in Ventricular Septal Defect	*Simon Dack*	199
The Roentgenographic Spectrum in Interventricular Septal Defect	*Dennison Young* *Bertha Rubinstein* *John B. Schwedel*	208
Considerations Involved in the Selection for Surgery of Patients with Ventricular Septal Defects	*S. Gilbert Blount, Jr.* *George M. Woodwark*	223
Surgical Treatment of Ventricular Septal Defects	*John W. Kirklin*	234
Results for Surgery of Ventricular Septal Defects	*Cid Nogueira* *Henry A. Zimmerman* *Earle B. Kay*	239
Current Research in Surgery of Ventricular Septal Defects	*Charles P. Bailey* *William M. Lemmon*	242
Sir William Broadbent on Pulseless Disease (1875)	*Saul Jarcho*	258
The Medical Use of Scales. An Historical Remark	*Bruno Kisch*	262
Treatment of Atrioventricular Block with Prednisone	*Zarko Caramelli* *Remo Ruiz Tellini*	263

Ventricular Septal Defect with Aortic Insufficiency. Successful Surgical Correction of Both Defects by the Transaortic Approach . . . . . *Joseph J. Garamella, Anatolio B. Cruz, Jr., William H. Heupel, James C. Dahl, Nathan K. Jensen, Reuben Berman* 266

Aorticopulmonary Septal Defect. Diagnosis and Report of Case Successfully Treated . . . . . *Ivan D. Baronofsky, Alvin J. Gordon, Arthur Grishman, Leonard Steinfeld, Isadore Kreel* 273

Obliterative Brachiocephalic Arteritis (Pulseless Disease) . . *T. J. Danaraj, Wong Hee Ong* 277

Ventricular Tachycardia. Importance of Differential Diagnosis in Evaluating Treatment . . . . . *William H. Wehrmacher* 280

Progress Notes in Cardiology 283

Cardiac Resuscitation 285

Query Corner 288

College News 289

March

The Hemodynamic Concept of Atherosclerosis . . . . . *Meyer Texon* 291

Absorption of I^{131}-Triolein in Congestive Heart Failure . . *Juha Hakkila, Touko E. Mäkelä, Pentti I. Halonen* 295

Cardiac Adrenergic Preponderance Due to Lack of Physical Exercise and Its Pathogenic Implications . . . . . *W. Raab, P. de Paula e Silva, H. Marchet, E. Kimura, Y. K. Starcheska, with the technical assistance of H. Deming, W. Lissauer, G. Marchet, E. Staudinger* 300

An Index for the Measurement of the Degree of Aortic Incompetence . . . . . *Ian F. S. Mackay* 321

Factors Affecting the Pulmonary "Capillary" Pressure . . *Bernard L. Charms, Bernard L. Brofman, Arnold Adicoff* 328

The "Straight Back" Syndrome. A New Cause of Pseudoheart Disease . . . . . *Maurice S. Rawlings* 333

The Electrocardiographic Findings in Pulmonary Emphysema *David Littmann* 339

The Vectorcardiogram in Chronic Chagas Myocarditis. An Analysis of the Intraventricular Conduction Delays Associated with a Superiorly Oriented ÂQRS . . . . . *Jozef Fèhér, Fúlvio Pileggi, Vitor Teixeira, João Tranchesi, Francisco Xavier Pinto Lima, Oswaldo Spiritus, Moris Chansky, Luiz V. Décourt* 349

A New Approach for the Recognition of Ventricular Premature Beats	*Abdo Bisteni, Demetrio Sodi-Pallares, Gustavo A. Medrano, Fúlvio Pileggi*	358
Heart Failure from the Point of View of Quantitative Anatomy	*A. J. Linzbach*	370
A New Concept of Cardiac Failure	*Bruno Kisch*	383
The Vectorelectrocardiogram. A Simple Method of Recording and Interpreting the Spatial Electrical Fields of the Heart	*J. Louis Freibrun, Julien H. Isaacs, George C. Griffith*	390
Hydroflumethiazide. The Clinical Pharmacology of a New Oral Diuretic	*Edward W. Dennis, Ralph V. Ford*	402
The Clinical Pharmacologic Investigation of a New Benzothiadiazine Diuretic, CMR-807	*Ralph V. Ford*	407
The Use of Hydroxyzine in the Prophylaxis and Therapy of Cardiac Arrhythmias	*Albert M. Ziffer, Solomon D. Klotz*	413
Maintenance Quinidine Therapy. Value of Enteric-Coated Quinidine Tablets	*David W. Richardson, Margaret E. Zee, Eugene M. Wyso*	417
Emotions and Angina Pectoris. An Historical Review	*Samuel J. Kowal*	421
Progress Notes in Cardiology		428
Book Reviews		431

April

Development of the Electrocardiographic Exercise Test. Standardized Versus Non-Standardized Test	*David Scherf*	433
The Evolution of the Vectorcardiogram and Electrocardiogram of the Normal Infant. I. The Normal Newborn	*Edwin L. Rothfeld, Fred W. Wachtel, William S. Karlen, Arthur Bernstein*	439
The Evolution of the Vectorcardiogram and Electrocardiogram of the Normal Infant. II. Transition Toward Adult Patterns	*Fred W. Wachtel, Edwin L. Rothfeld, William S. Karlen, Arthur Bernstein*	450
The Normal Vectorcardiogram of Children	*Eliot Young, Jerome Liebman, Alexander S. Nadas*	457
A Study of the Ventricular Gradient in Normal Infants and Children	*Nicholas P. DePasquale, George E. Burch*	464
Observations on the T Wave and S-T Segment Changes in the Precordial Electrocardiogram of 320 Young Negro Adults	*John Thomas, Evelyn Harris, Genora Lassiter*	468
Electrocardiographic Changes Produced by the Valsalva Maneuver in Healthy Adults	*Norman Shaftel, David Selman, Paul H. Kuhn, Alfred Halpern*	473

Postoperative Changes in Blood Coagulation in Elderly Patients	*Giorgio Feruglio* *Hershel Sandberg* *Samuel Bellet*	477
Comparison of Internal Mammary Artery Ligation and Sham Operation for Angina Pectoris	*E. Grey Dimond* *C. Frederick Kittle* *James E. Crockett*	483
Acute Myocardial Infarction in a City Hospital. III. Experience with Shock	*Monte Malach* *Benjamin A. Rosenberg*	487
Retrograde Arterial Catheterization of the Left Ventricle	*Gerardo Voci* *Neil A. J. Hamer*	493
The Effect of Quinidine on Tolerance to Digoxin	*Paul L. Rodensky* *John H. Kathe* *Fred Wasserman*	498
The Electrocardiogram During Exercise	*Alvin H. Freiman* *William Tolles* *William J. Carberry* *Paul Ruegsegger* *Ramon F. Abarquez* *John S. LaDue*	506
An Approach to the Action of the Cardiac Glycosides at a Cellular Level	*John C. Krantz, Jr.* *Johnson S. L. Ling*	516
The Toxicology of Digitalis	*Andrew P. Somlyo*	523
Obstruction of the Thoracic Duct by Aortic Aneurysm (Turner, 1859; Laennec, 1806)	*Saul Jarcho*	534
Therapy of Stokes-Adams Syndrome. Report of Four Unusual Cases, with a Review of the Literature	*Theodore H. Goldberg* *Robert S. Palman*	540
Left Aortic Arch (Posterior or Circumflex Type) with Right Descending Aorta	*R. Heim de Balsac*	546
Simultaneous Surgical Treatment of Coexistent Coarctation of the Aorta and Aortic Valvular Stenosis	*P. Carrillo Rivera* *Howard L. Gadboys* *Robert P. Glover*	551
Glycogen Storage Disease of the Heart. First Case in Japan	*Takajiro Yamamoto* *Atsuhisa Eguchi* *Masahiko Okudaira* *Eiko Suzuki* *Takeshi Yokoyama* *Junichi Tanabe*	556
Pulmonary Artery Aneurysm with Dissection After Blalock Operation for Tetralogy of Fallot	*Samuel Epstein* *Abdul F. Naji*	560
Dissociation of Pacemakers Located within the Atrioventricular Node	*Robert B. Chevalier* *Charles Fisch*	564
The Query Corner		566
College News		567

May

Key Position of Catecholamines in Functional and Degenerative Cardiovascular Pathology	*W. Raab*	571

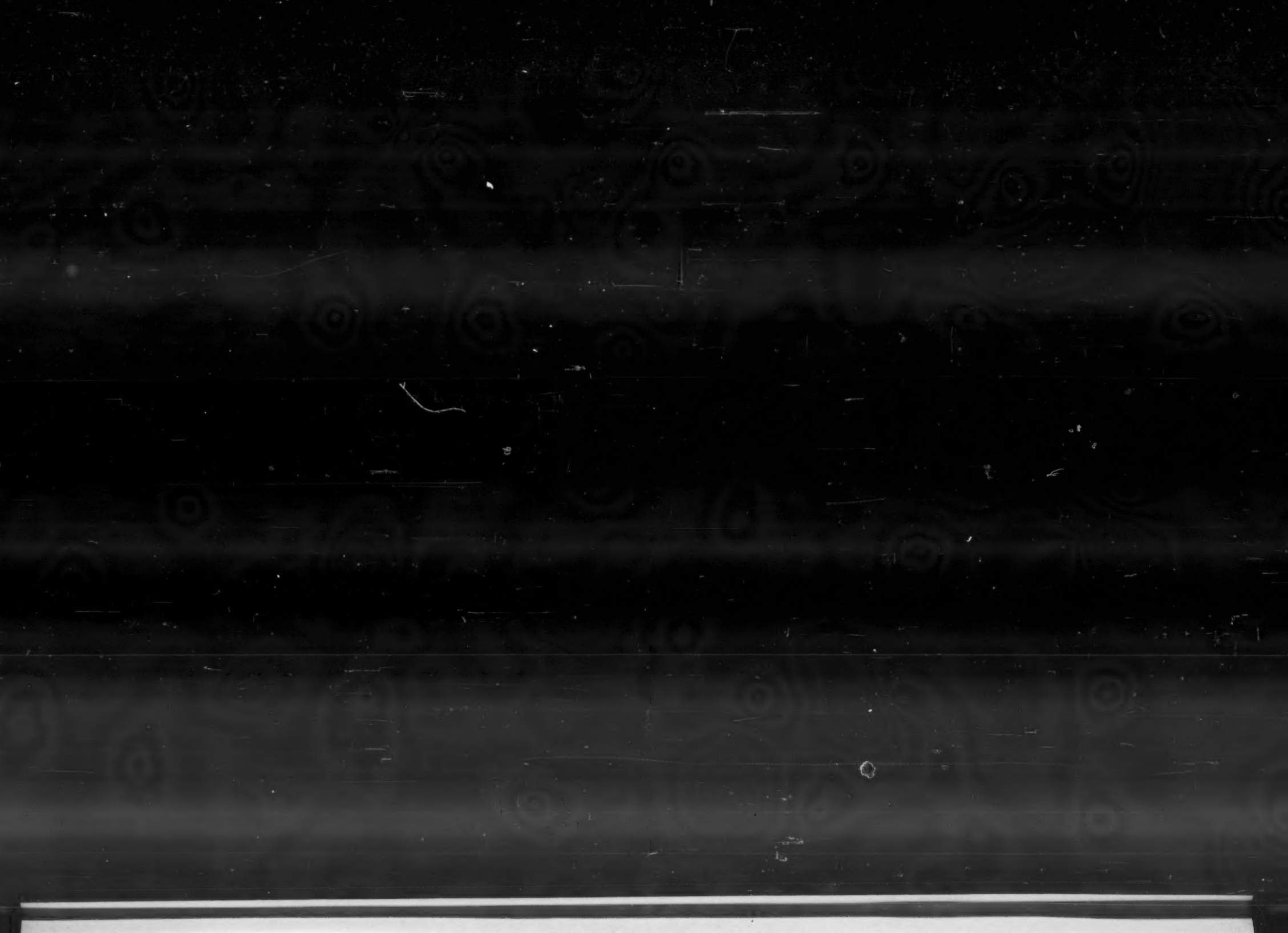
Certain Aspects of the Role of Catecholamines in Circulatory Regulation	*Stanley J. Sarnoff*	579
Influence of Sympathetic Stimulation and Catecholamines on Ectopic Impulse Formation in the Ventricles of the Dog	*David Scherf*	589
Effect of Epinephrine and Norepinephrine on the Electrocardiogram of 100 Normal Subjects	*E. Lepeschkin* *H. Marchet* *G. Schroeder* *R. Wagner* *P. de Paula e Silva* *W. Raab* *with the technical assistance of* *Y. K. Starcheska*	594
The Adrenosympathetic and Adrenocortical Function in Cardiac Insufficiency	*A. Pekkarinen* *E. Iisalo* *A. Kasanen* *A. Laihinen* *B. Thomasson*	604
Circulating Epinephrine and Norepinephrine in Coronary Occlusion	*J. A. Richardson* *E. F. Woods* *E. E. Bagwell* *with the technical assistance of* *Douglas C. Owens* *Algie C. Brown* *Marcy S. Walsh*	613
Pathologic Changes Induced by 1-Norepinephrine	*Lt. Comdr. Jenö E. Szakacs* *Benjamin Mehlman*	619
Some Similar Effects After Large Doses of Catecholamines and Myocardial Infarction in Dogs	*Harriet M. Maling* *Benjamin Highman* *Edwin C. Thompson* *with the assistance of* *William M. Butler, Jr.* *Martha A. Williams*	628
Amine Oxidase Inhibitors in the Treatment of Angina Pectoris. Preliminary Report on Marplan and Tersavid	*William B. Abrams* *Marvin C. Becker* *Daniel W. Lewis* *John H. Killough*	634
The Influence of Antihypertensive and Hypertensive Substances on Vascular Reactivity to Catecholamines	*A. J. Plummer* *F. F. Yonkman*	640
The Nature of the Increased Peripheral Resistance in Hypertension	*James Conway*	649
The Effects of Various Catecholamines on Specific Vascular Hemodynamics in Hypotensive and Normotensive Subjects	*Lewis C. Mills* *John H. Moyer*	652
Studies on Vasoactivity of Catecholamines in Man	*Walter Redisch* *Kurt de Crinis* *J. Murray Steele* *with the technical assistance of* *William Brown*	660
Studies of Inhibition of the Plasmin-Plasminogen Fibrinolytic Enzyme System in Patients with Myocardial Infarction	*Herschel Sandberg* *George Tsitouris* *Antonio C. deLeon, Jr.* *Samuel Bellet* *with the technical assistance of* *Jean Schraeder*	666

The Fibrinolytic System and Use of Fibrinolysin in Myocardial Infarction. Preliminary Report	*Antonio C. deLeon, Jr.* *Samuel Bellet* *George Tsitouris* *Leonard E. Lecks* *Herschel Sandberg*	674
Studies of the Plasmin-Plasminogen System in Thromboembolic Diseases. Its Modifications by Thrombolysin Therapy	*George Tsitouris* *Herschel Sandberg* *Antonio C. deLeon, Jr.* *Leonard Lecks* *Samuel Bellet* *with the technical assistance of* *Jean Schraeder*	680
Peripheral Distribution of the Canine A-V Conduction System. Observations on Gross Morphology	*Herman N. Uhley* *Laurence Rivkin*	688
Diagnostic and Pathogenic Borderlines Between Hypertensive Disease and Atherosclerosis	*Prof. A. L. Miasnikov*	692
Piorry on Percussion of the Heart	*Alfredo Buzzi*	703
Letter to the Editor		706
Abstracts		707
College News		720

June

Treatment of Cardiovascular Emergencies	*Aldo A. Luisada*	725
Ejection Time in Aortic Stenosis and Mitral Stenosis. Comparison Between the Direct and Indirect Arterial Tracings, with Special Reference to Pre- and Postoperative Findings	*Alberto Benchimol* *E. Grey Dimond* *Yen Shen*	728
Pulmonic Stenosis. A Clinical Assessment of Severity	*Joseph H. Yahini* *Maurice J. Dulfano* *Mordecai Toor*	744
Aortic Valve Insufficiency in Arterial Hypertension	*Thomas C. Puchner* *John H. Huston* *George A. Hellmuth*	758
Patent Ductus Arteriosus and High Altitude	*Victor Alzamora-Castro* *Guido Battilana* *Ricardo Abugattas* *Salvador Sialer*	761
The Double Femoral Sound	*Victor Alzamora-Castro* *Guido Battilana*	764
The Neuropsychiatric Impact and Psychologic Significance of Cerebrovascular Damage (Strokes) Following Rheumatic Heart Surgery	*Misha S. Zaks* *J. Lachman* *G. K. Yacorzynski* *B. Boshes*	768
Problems Associated with the Use of Antibiotics for the Prevention of Primary Episodes of Rheumatic Fever	*Milton S. Saslaw* *James M. Jablon* *Sallie Anne Jenks* *with the technical assistance of* *Claudette Branch*	777
Coronary Nodal Rhythm	*Edward J. Eyring* *David H. Spodik*	781

Lipid Measurements in Coronary Artery Disease. Comparison with an Age-Matched Normal Control Group	*Arthur U. Rivin* *Herbert Wong* *with the technical assistance of* *Josephine Yoshino*	784
Ventriculo-Ventricular Dissociation	*B. Malamos* *S. Moulopoulos*	789
The Influence of Quinidine and Procaine Amide on Myocardial Contractility in Vivo	*Evangelos T. Angelakos* *Elliott P. Hastings*	791
Experimental Bilateral Bundle Branch Block	*William H. Bernstein* *Philip Samet* *Robert S. Litwak*	799
Preliminary Evaluation of Ro 2-5803—An Antiarrhythmic Agent	*Robert S. Green* *Paul G. Geiss* *Ali Sumen* *Joseph Schuster*	806
Preliminary Observations on a New Antiarrhythmic Agent (Ro 2-5803)	*Albert N. Brest* *Jane Straughn* *Alvin Singer* *William Likoff*	811
Mitral Stenosis. Auscultatory and Phonocardiographic Findings	*Simon Dack* *Selvyn Bleifer* *Arthur Grishman* *Ephraim Donoso*	815
The Auscultatory and Phonocardiographic Findings in Mitral Regurgitation	*Selvyn Bleifer* *Simon Dack* *Arthur Grishman* *Ephraim Donoso*	836
Armand Trousseau on Acute Articular Rheumatism	*Saul Jarcho*	843
Chronic Subclavian-Carotid Artery Obstruction Syndrome. Report of a Patient with Coarctation of the Aorta and Rupture of an Associated Traumatic Aneurysm of the Aortic Arch	*Bernard Chojnacki* *Remberto Rangel* *Frederick S. Cross*	849
Combined Congenital Pulmonic and Aortic Stenosis	*Henry N. Neufeld* *M. Hirsch* *J. Pauzner*	855
Aortic Stenosis vs. Syphilitic Aortitis	*Aldo A. Luisada* *Jan Szatkowski*	860
Progress Notes in Cardiology		862
Workmen's Compensation for the Cardiac		864
Author Index		867
Subject Index		869



The American Journal of

CARDIOLOGY

OFFICIAL JOURNAL OF THE American College of Cardiology

Coronary Disease and Myocardial Infarction

Copy 2
Lane Library

A PUBLICATION OF THE Yorke GROUP

JANUARY 1960

Used in every type of practice and clinical specialty today, EQUANIL® (meprobamate, Wyeth) has proved that anxiety and tension *can* be controlled to smooth the course of diagnosis, treatment, and convalescence. Anxiety is a fact of life. Anxiety is a fact of illness.

Wyeth®
Philadelphia 1, Pa

The true measure of this dramatically new Cardi-O-Mite is its unsurpassed accuracy and versatility...backed by more than a quarter-century of manufacturing electrocardiographs exclusively. Among the advanced engineering achievements of Cardi-O-Mite are audible monitoring; visual monitoring; choice of 25mm and 50mm speeds; ultra-simple one-hand operation; and all standard leads on full-size 6 cm recording paper in an electrocardiograph that measures only 11-1/2" x 7-1/2" x 6-1/2" and weighs only 17 pounds! A two year guarantee on the entire instrument includes all components and accessories. See for yourself why the entirely new Beck-Lee Cardi-O-Mite is unsurpassed by any other EKG. Write for the name of your nearest dealer.

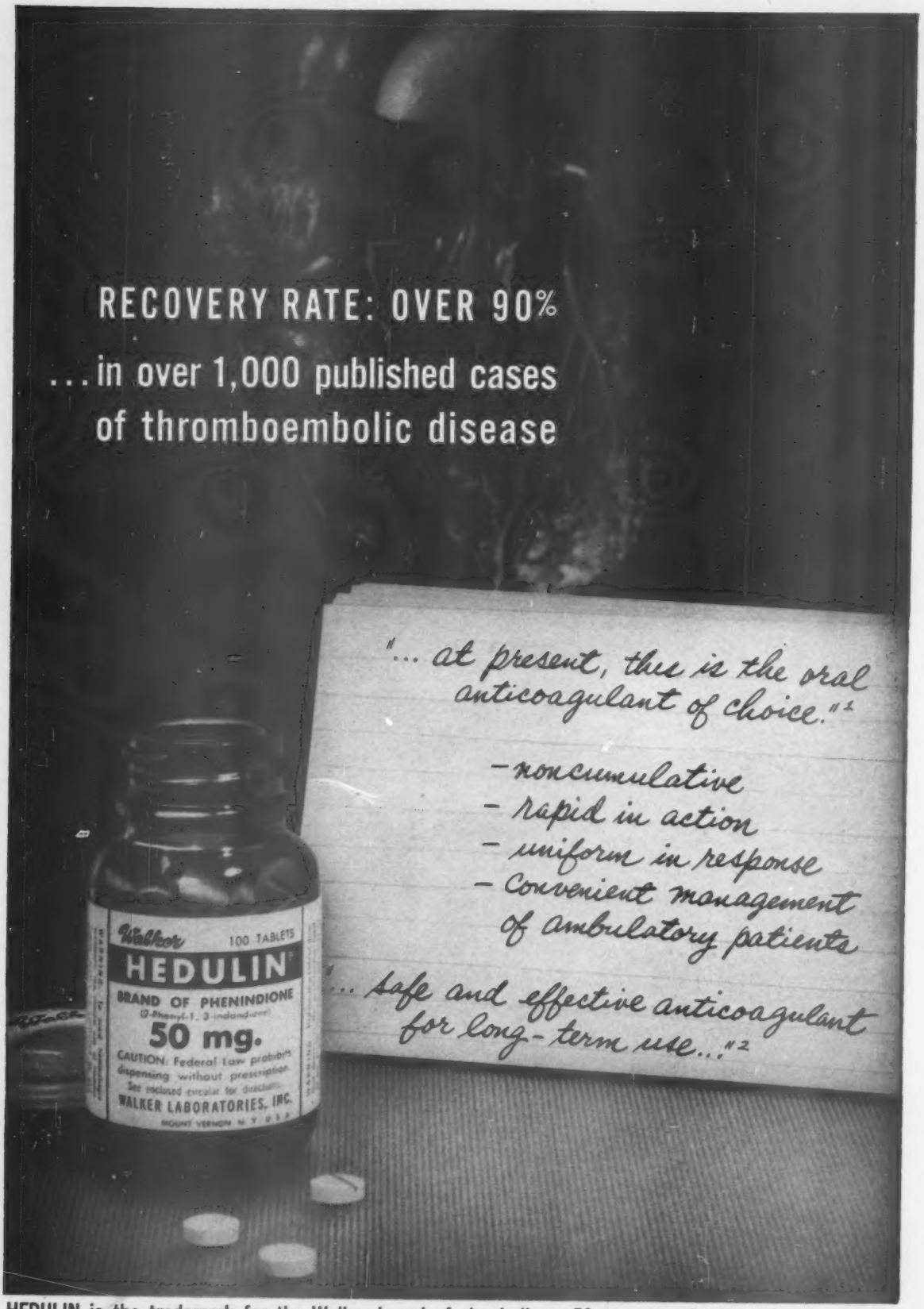
Cardi-O-Mite

masterpiece in design and performance

BECK-LEE CORPORATION

DEPT. AJC160, 630 W. JACKSON BLVD., CHICAGO 6, U.S.A.

World's Largest Exclusive Manufacturer of Electrocardiographs—Quartz-String and Cardi-all Direct Writing


RECOVERY RATE: OVER 90%
... in over 1,000 published cases
of thromboembolic disease
"... at present, this is the oral anticoagulant of choice."[1]
- noncumulative
- rapid in action
- uniform in response
- convenient management of ambulatory patients
"... safe and effective anticoagulant for long-term use..."[2]
Walker
100 TABLETS
HEDULIN
BRAND OF PHENINDIONE
50 mg.
CAUTION: Federal law prohibits dispensing without prescription
See inclosed circular for directions
WALKER LABORATORIES, INC.

HEDULIN is the trademark for the Walker brand of phenindione. 50 mg. scored tablets for therapeutic use; 20 mg. scored tablets for prophylactic use. Bottles of 100 and 1,000. For more detailed information and a clinical trial supply of Hedulin, write to Walker Laboratories, Inc., Mount Vernon, N. Y.

1. Breneman, G. M., and Priest, E. McC.: Am. Heart J. 50:129 (July) 1955. 2. Tandowsky, R. M.: Am. J. Cardiol. 3:551 (April) 1959.

The American Journal of Cardiology

Editor-in-Chief
SIMON DACK, M.D., NEW YORK

Associate Editors

ASHTON GRAYBIEL, M.D.
PENSACOLA

GEORGE R. MENEELY, M.D.
NASHVILLE

ALDO A. LUISADA, M.D.
CHICAGO

MYRON PRINZMETAL, M.D.
LOS ANGELES

Assistant Editors

RAYMOND HARRIS, M.D.
ALBANY

LESLIE A. KUHN, M.D.
NEW YORK

EDITORIAL CONSULTANTS

Osler A. Abbott, M.D., *Atlanta*
Mariano M. Alimurung, M.D., *Manila*
Charles P. Bailey, M.D., *Philadelphia*
Claude S. Beck, M.D., *Cleveland*
Richard J. Bing, M.D., *Detroit*
Benjamin Boshes, M.D., *Chicago*
Ignacio Chávez, M.D., *Mexico City*
Eduardo Coelho, M.D., *Lisbon*
Pedro Cossio, M.D., *Buenos Aires*
J. Frank Dammann, Jr., M.D., *Charlottesville*
David B. Dill, M.D., *Army Chemical Center*
Felix G. Fleischner, M.D., *Boston*
Benjamin M. Gasul, M.D., *Chicago*
Robert P. Glover, M.D., *Philadelphia*
John W. Gofman, M.D., *Berkeley*
Emanuel Goldberger, M.D., *New York*
E. Magalhaes Gomes, M.D., *Rio de Janeiro*
Donald E. Gregg, M.D., *Washington*
Arthur Grishman, M.D., *New York*
Arthur C. Guyton, M.D., *Jackson*
W. F. Hamilton, PH.D., *Augusta*
R. Heim de Balsac, M.D., *Paris*
Herman E. Hilleboe, M.D., *Albany*
Martti J. Karvonen, M.D., *Helsinki*
Bruno Kisch, M.D., *New York*
Ray W. Kissane, M.D., *Columbus*
H. W. Knipping, M.D., *Cologne*
John C. Krantz, Jr., M.D., *Baltimore*
Philip R. Lee, M.D., *Palo Alto*
Samuel A. Levine, M.D., *Boston*
William Likoff, M.D., *Philadelphia*
K. I. Melville, M.D., *Montreal*
M. Carlos Monge, M.D., *Lima*
Alexander S. Nadas, M.D., *Boston*
John L. Patterson, Jr., M.D., *Richmond*
Arrigo Poppi, M.D., *Bologna*
Walter S. Priest, M.D., *Chicago*
Wilhelm Raab, M.D., *Burlington*
Fernando Herrera Ramos, M.D., *Montevideo*
Stanley J. Sarnoff, M.D., *Bethesda*
G. W. H. Schepers, M.D., *Wilmington*
David Scherf, M.D., *New York*
Hans Selye, M.D., *Montreal*
Louis H. Sigler, M.D., *Brooklyn*
Demetrio Sodi-Pallares, M.D., *Mexico City*
Pierre Soulié, M.D., *Paris*
Paul Wood, M.D., *London*
Henry A. Zimmerman, M.D., *Cleveland*

The American Journal of Cardiology is published monthly by The American Journal of Cardiology, Inc., 11 East 36th Street, New York 16, N. Y. Yearly Subscription $12.00 U. S. A.; $13.00 Canada; $15.00 Foreign. Single Numbers $2.00; Symposium Numbers $4.00. Second-class postage paid at New York, N. Y. and at additional mailing offices. January 1960—Volume V, No. 1.

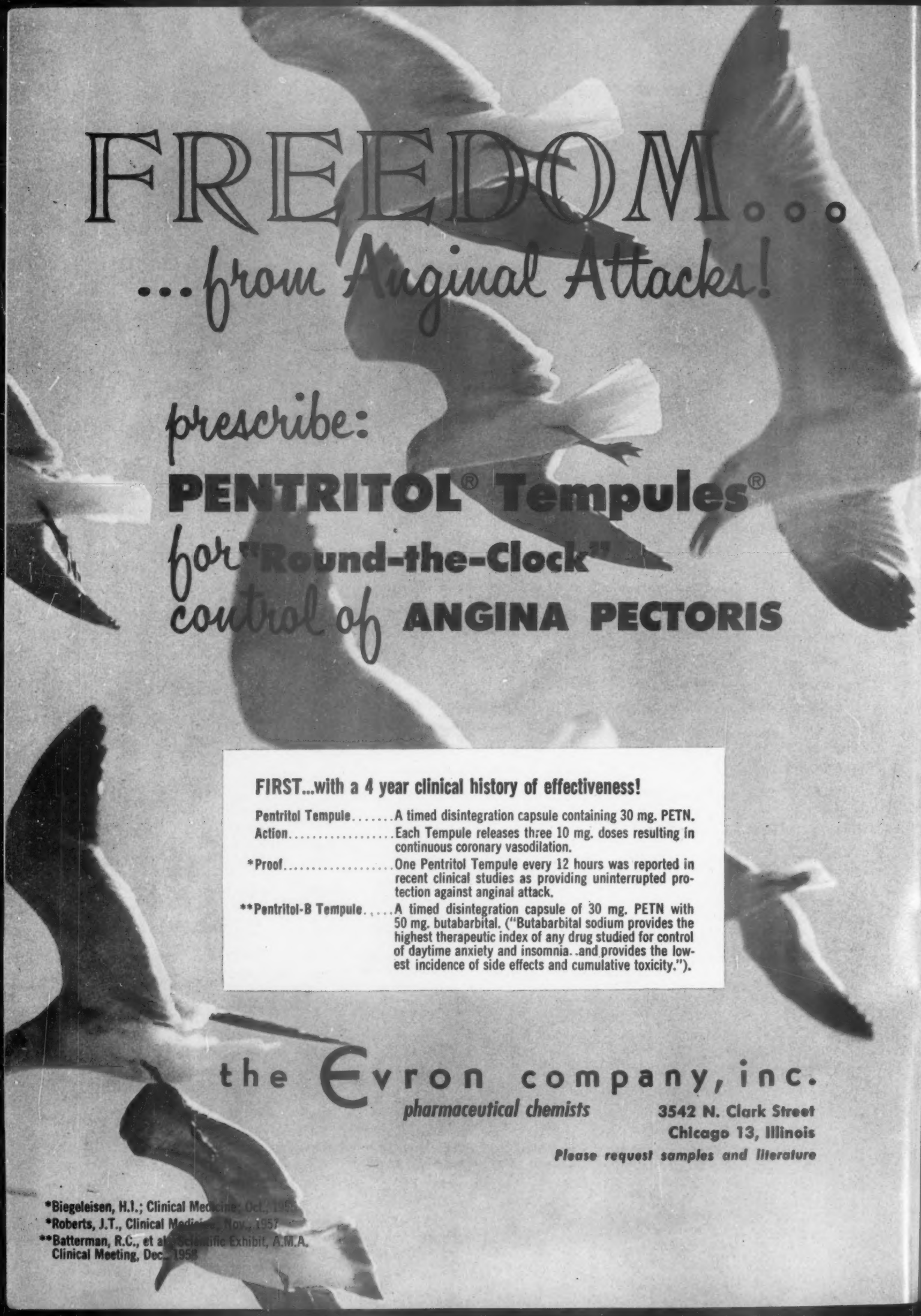
Copyright © 1960 by The American Journal of Cardiology, Inc. No part of the contents of this publication may be reproduced or distributed without the express written consent of the publishers.

MANUSCRIPTS: All manuscripts should be typewritten, double spaced, and submitted in duplicate to the Editorial Office of the Journal, 11 East 36th Street, New York 16, N. Y. Style for References: Smith, J. S. Treatment of cardiac failure. *Am. J. Cardiol.*, 3:274, 1959.

AMERICAN COLLEGE OF CARDIOLOGY: All communications for the College should be addressed to the American College of Cardiology, Office of the Executive Director, 350 Fifth Avenue, New York 1, New York.

Change of address must reach us one month preceding month of issue.

ADVERTISING REPRESENTATIVES: New York: P. A. Porter, P. D. Brewer, H. S. Schultz, A. K. Detwiller MUrray Hill 3-2980. Chicago: R. H. Andrew, C. P. Haffner, FRanklin 2-3861


FREEDOM...
...from Anginal Attacks!
prescribe:
PENTRITOL® Tempules®
for "Round-the-Clock"
control of ANGINA PECTORIS
FIRST...with a 4 year clinical history of effectiveness!
Pentritol Tempule.....A timed disintegration capsule containing 30 mg. PETN.
Action.....Each Tempule releases three 10 mg. doses resulting in continuous coronary vasodilation.
*Proof.....One Pentritol Tempule every 12 hours was reported in recent clinical studies as providing uninterrupted protection against anginal attack.
**Pentritol-B Tempule.....A timed disintegration capsule of 30 mg. PETN with 50 mg. butabarbital. ("Butabarbital sodium provides the highest therapeutic index of any drug studied for control of daytime anxiety and insomnia...and provides the lowest incidence of side effects and cumulative toxicity.").
the Evron company, inc.
pharmaceutical chemists
3542 N. Clark Street
Chicago 13, Illinois
Please request samples and literature
*Biegeleisen, H.I.; Clinical Medicine: Oct., 1958
*Roberts, J.T., Clinical Medicine, Nov., 1957
**Batterman, R.C., et al: Scientific Exhibit, A.M.A. Clinical Meeting, Dec., 1958

The American Journal of Cardiology

Volume V JANUARY 1960 Number 1

CONTENTS

Editorials

Surgical Treatment of Angina . . . . . WILLIAM DOCK 1

Clinical Studies

Thromboendarterectomy for Coronary Artery Disease
CHARLES P. BAILEY, DRYDEN P. MORSE AND WILLIAM M. LEMMON 3

Coronary artery disease is a ubiquitous condition treated somewhat fatalistically by philosophic physicians and more intrepidly by energetic cardiac surgeons. New surgical approaches to the heart vessels have added important knowledge about coronary artery disease even if they have not significantly lowered the over-all mortality of the disease. This article presents the indications and contraindications for coronary endarterectomy or thromboendarterectomy and the results in fifteen patients between twenty-eight and thirty-five years of age. The authors conclude that this operation is technically possible with excellent results in properly selected patients. The value of coronary angiography preoperatively is emphasized.

Rupture of the Heart in Myocardial Infarction. Clinical and Pathologic Observations
LOUIS H. SIGLER 14

Observations on rupture of the heart in eight patients with myocardial infarction and a review of the literature are presented. One or more of the underlying predisposing factors are pre-existing and co-existing hypertension with its strain on the heart and hypertrophy of the myocardial fiber, the female sex in which hypertension is more common, the older age group, early age of the infarct, local enzymatic destruction and the location of the coronary occlusion, usually in the anterior descending branch of the left coronary artery. Anticoagulant and digitalis therapy is less likely to be implicated.

Disturbances of Rate, Rhythm and Conduction in Acute Myocardial Infarction. A Statistical Study of 153 Cases
ELIAS S. IMPERIAL, RODOLFO CARBALLO AND HENRY A. ZIMMERMAN 24

Some disturbance in rate, rhythm and conduction occurred in 73.2 per cent of 153 patients with acute myocardial infarction. The mortality rate of patients with some form of disturbance was considerably higher than the over-all mortality rate. It varied significantly with different types of disturbances but not with different locations of the infarct. Prognosis in acute myocardial infarction can be judiciously based on evaluation of the cardiac rhythm.

Thumping of the Precordium in Ventricular Standstill
DAVID SCHERF AND CARL BORNEMANN 30

Mechanical stimulation of the heart by blows "fair on the breastbone" is recommended as a routine measure to re-establish automaticity in ventricular standstill while mouth-to-mouth breathing is employed and other methods, such as electrical stimulation or the use of certain pressor amines, are prepared. The blows preserve life by evolving ectopic beats which may reawaken cardiac automatism. Results of this method in eleven patients demonstrated the value of this long-known but little used simple maneuver.

Incidence of Myocardial Infarction Correlated with Venous and Pulmonary Thrombolis and Embolism . . . . . WILBUR A. THOMAS, JACK N. P. DAVIES, ROBERT M. O'NEAL AND AMADOR A. DIMAKULANGAN 41

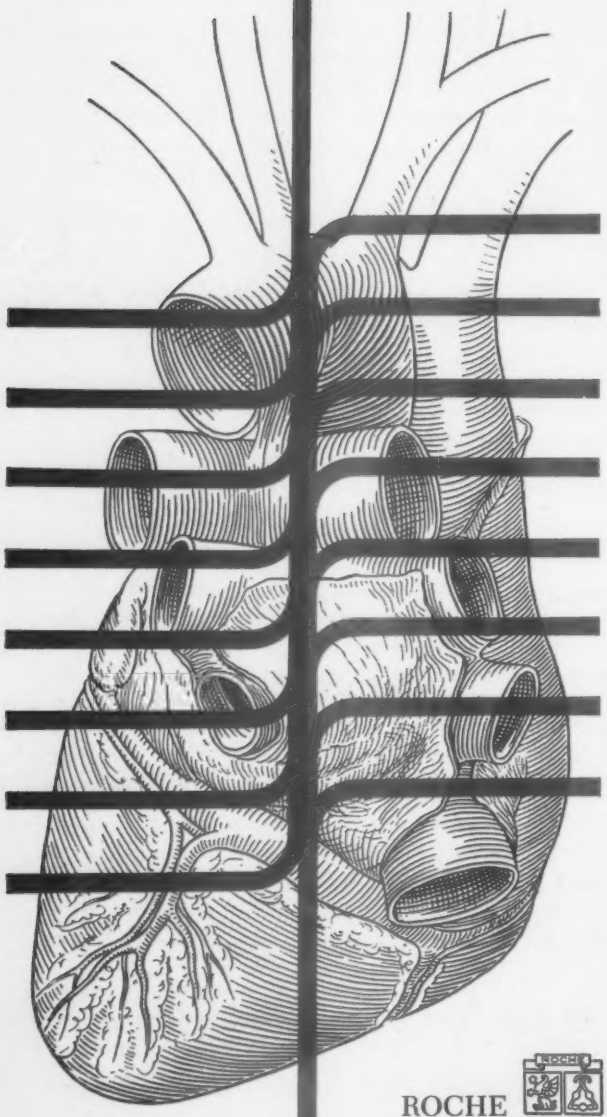
This geographical study based on a review of well matched recent autopsy records at Washington University in St. Louis and Makerere College in Uganda, East Africa shows that the incidence of myocardial

Contents continued on page 7

new approach to the concept of "total management" in angina pectoris

new Marplan

a happy balance of potency/safety



Marplan prevents or reduces anginal pain: Marplan is indicated primarily for patients with moderately severe to intractable angina pectoris. It has demonstrated a high degree of effectiveness. When used on a continuous dosage schedule, Marplan prevents pain, increases exercise tolerance and reduces nitroglycerin requirements.

Marplan creates a more confident mental climate: Many angina patients display a more cheerful outlook when on Marplan therapy. This mental improvement is undoubtedly due to the antidepressive action of Marplan. However, it should be stressed that Marplan is indicated for *symptomatic* control of angina pectoris. While it abolishes anginal pain (some patients may achieve a virtually pain-free state), Marplan does not appear to influence the EKG. Hence, as with previously available prophylactic agents, it is imperative that patients be instructed to maintain the same restriction of activity in force prior to Marplan therapy.

Marplan strikes a happy balance of potency/safety: Marplan has been shown to be considerably more potent than certain other amine oxidase regulators. While clinically such increase in potency may be associated with increased side effects, Marplan strikes a happy balance of potency/safety. Marplan has shown markedly fewer of certain of the side reactions of the hydrazines and, moreover, throughout extensive clinical investigations, no liver damage attributable to Marplan therapy has been reported. Marplan is an amine oxidase regulator, however, and like all of these agents, it is contraindicated in the presence of liver or kidney disease.

Consult literature, dosage instructions, available on request, before prescribing.

ROCHE LABORATORIES
Division of Hoffmann-La Roche Inc.
Nutley 10, N.J.

MARPLAN™ — brand of isocarboxazid
ROCHE®

CONTENTS continued—January 1960

infarcts was high in St. Louis white patients, intermediate in St. Louis Negroes and practically nil in Uganda Negroes. Only one infarct was found in 1,427 patients over forty years of age in the African Negroes. The incidence of venous thrombi and pulmonary thromboembolic phenomena closely paralleled the incidence of myocardial infarcts in the three groups. These results suggest that differences in the general tendency of the blood to clot and/or lyse account for the differences in the incidences of coronary thrombosis and myocardial infarction. Differences in the degree of atherosclerosis present in the three groups may also contribute to the differences in incidences of myocardial infarction, but since the local factor of atherosclerosis is not present in veins, it could not account for the observed differences in venous thrombosis.

Coronary Heart Disease in the South African Bantu
W. Laurie, J. D. Woods and G. Roach 48

This clinicopathologic study of coronary heart disease in the South African Bantu found the incidence of proved frank myocardial infarction was about 1.4 per cent, an incidence higher than that reported by other workers in Africa, but much lower than in European patients. In the Bantu the more common mode of onset of ischemic myocardial disease is by minute infarcts which cause patchy fibrosis of the myocardium and resultant cardiac failure. Although the Bantus have narrowed and atherosclerotic coronary vessels, they apparently do not readily develop clotting in the main coronary branches, possibly due to elevated plasma fibrinolytic activity. Angina pectoris is not uncommon and may occur in patients with syphilitic aortic disease and coronary atherosclerosis.

Problem of Heart Disease in India . . . . . K. S. Mathur 60

This article on heart disease in India dispels some common misconceptions about the evidence and frequency of heart disease in India and reports reliable first-hand observations. It is a good contribution to international knowledge of the epidemiology of heart disease. Rheumatic heart disease heads the list of cardiovascular diseases in India in the hospital class of patients; hypertensive and coronary heart disease still account for the majority of private cases which belong to upper and middle socioeconomic groups. The increasing incidence of these so-called degenerative heart diseases, in India as elsewhere, poses a great challenge. The incidence of pulmonary heart disease in this series is surprisingly high.

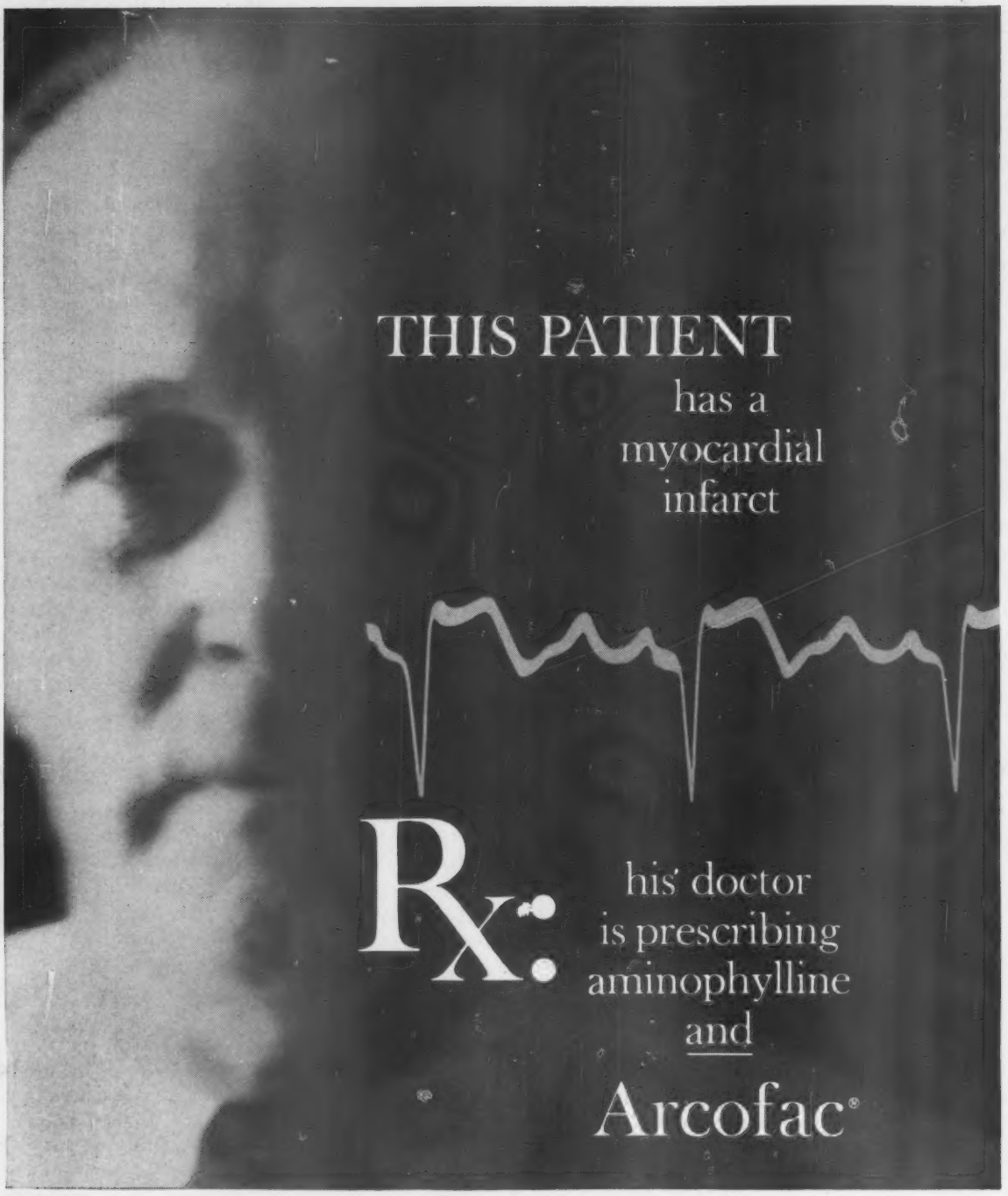
A Pharmacodynamic Approach to the Evaluation of Nitrites in the Treatment of Angina Pectoris . . . . . Irving Hirshleifer 66

The writer suggests that the segmental plethysmograph, by indicating volume changes with each cardiac pulsation, offers an opportunity for a truly objective pharmacodynamic approach to the evaluation of nitrites in angina pectoris. Plethysmographic records offer direct evidence that with nitroglycerine or erythrol tetranitrate, sublingual or oral routes of administration are essentially equivalent in producing the desired therapeutic effect. Sublingual nitroglycerine tablets may take from thirty seconds to as long as eight minutes to disintegrate. The more extended disintegration time is particularly true for older age groups.

Plethysmographic Studies in Atherosclerosis Obliterans . . . Alfredo Buzzi 72

The abnormalities of digital pulse volume recorded plethysmographically are described and classified on the basis of pulse volume contour into three grades. Grade 1 curves have a rounded peak, absent dicrotic phenomena, a sinusoidal shape and normal amplitude. Grade 2 curves have in addition to the morphologic abnormalities of grade 1, a toe pulse volume reduced usually to half of normal. Grade 3 curves have marked flattening with meager amplitudes. Close correlation exists between the arteriosclerotic lesions as demonstrated by arteriography and the plethysmograms. These curves have value in the estimation of vascular reserves, the preoperative selection for grafting arterial surgery, determination of the results of medical and surgical treatment, and prognosis.

Contents continued on page 9



©A.P. Co.

Arcofac is an important additional safeguard
to prevent or control hypercholesteremia

EVERY MYOCARDIAL PATIENT MAY WELL DESERVE THE ADDITIONAL PROTECTION AFFORDED BY ARCOFAC

Arcofac (Armour Cholesterol Lowering Factor) lowers elevated blood cholesterol levels, safely, effectively and without imposing radical dietary changes.

Each tablespoonful (15 ml.) of Arcofac contains:
Essential fatty acids* . . . . . 6.8 Gm.
(measured as linoleic) with 2.5 I.U. of Vitamin E†
Pyridoxine hydrochloride (Vitamin B_6) . . . 1.0 mg.

*Supplied by safflower oil which contains the highest concentration of polyunsaturated fatty acids of any commercially available vegetable oil.
†Added as Mixed Tocopherols Concentrate, N.F.

ARMOUR PHARMACEUTICAL COMPANY
KANKAKEE, ILLINOIS *Armour Means Protection*

CONTENTS continued—January 1960

VOLUME FIVE NUMBER ONE

Experimental Studies

Ventricular Fibrillation During and After Coronary Artery Occlusion. Incidence and Protection Afforded by Various Drugs . . . . SAM E. STEPHENSON, JR., RICHARD K. COLE, THOMAS F. PARRISH, FRANK M. BAUER, JR., IRA T. JOHNSON, JR., MORSE KOCHTITZKY, JAMES S. ANDERSON, JR., LESTER L. HIBBITT, JAMES E. MCCARTY, EDWIN R. YOUNG, JOHN R. WILSON, HENRY N. MEIERS, CLIFTON K. MEADOR, CON O. T. BALL AND GEORGE R. MENEELY 77

The incidence of ventricular fibrillation during and after temporary experimental occlusion of the left anterior descending coronary artery or its branches was studied in 351 untreated dogs and then in 324 dogs treated with various drugs possessing antiarrhythmic properties. Quinidine was the most effective drug in affording protection from ventricular arrhythmia during and following occlusion. Procaine, procaine amide and Apresoline offered good protection during the ischemic period. Apresoline and Regitine also reduced the incidence of ventricular fibrillation upon reopening the ligature. Pendiomide also significantly reduced the incidence of fibrillation on release of the artery. Paveril, adenosine triphosphate, Priscoline, Trasentine and Xylocaine were of little or no value under the conditions of this study. Systemic arterial pressures were unrelated to the onset of ventricular arrhythmia. Electrical countershock accomplished cardiac resuscitation in 75 per cent of the fibrillating dogs.

Recovery of Peripherally Injected Materials from the Heart at Varying Intervals after Death . . . . . IRA N. ROSENSTEIN AND FRED WASSERMAN 88

The growing importance of cardiac resuscitation spurred these investigators to a novel study of the circulation after death. Employing colorimetrically assayable dyes, radioisotopes and radiopaque materials, they demonstrated that these substances, injected into the peripheral veins of dogs at varying intervals postmortem, reach the right side of the heart. Intravenous administration is more effective in the closed chest where "negative" intrathoracic pressures persist than in the open chest. This study provides a rationale for the use of intravenous medications to supplement the effect of prolonged cardiac massage or other treatments to resuscitate the fibrillating or asystolic heart.

Franz Groedel Memorial Lecture

The History of Coronary Sclerosis . . . . . PAUL KLEMPERER 94

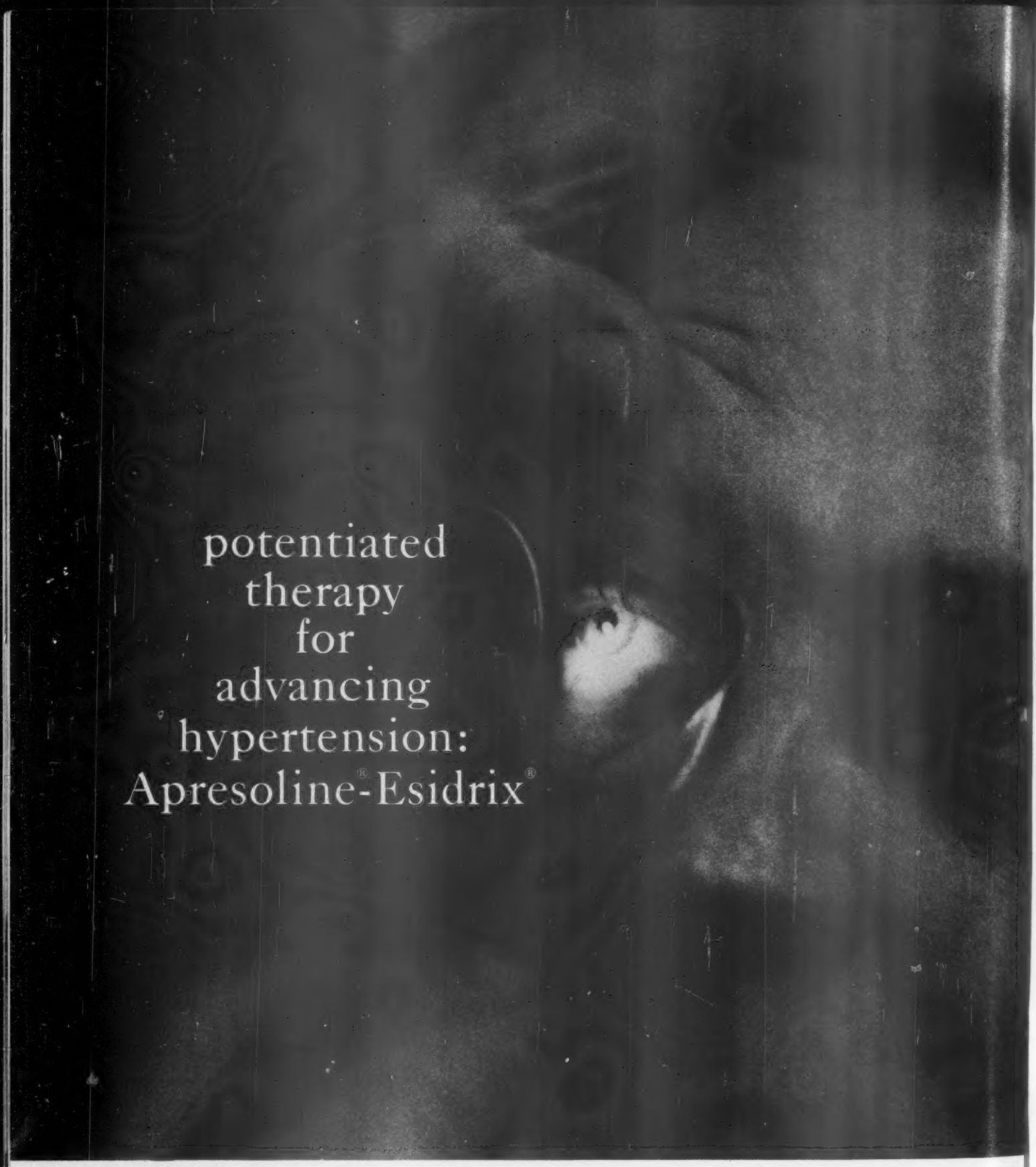
This lecture surveys the important achievements in the long history of coronary sclerosis which resulted from the interplay of exact bedside and autopsy observations and rational thought. Written in a fresh style, this article throws sharper light on the various facets of an important complex medical problem. The perspective of history enables this eminent pathologist to bestow credit, albeit belated, to many workers in this field whose contributions were lost or overlooked in the medical literature. Two such physicians were Bartoletti (1576–1630) and Burns (1781–1813). The former described a clinical syndrome resembling angina pectoris while the latter, by observation and experiment, clearly recognized that heart pain resulted from muscular ischemia. Unfortunately, the crucial problem, the etiology of coronary sclerosis, formulated 160 years ago by Parry, still awaits solution today.

Report on Therapy

Comparison of Laxative Action of Bisacodyl Suppositories and Glycerin Suppositories in Acute Myocardial Infarction . JULES LEVINE AND SEYMOUR H. RINZLER 108

Constipation frequently complicates acute myocardial infarction. In this study a new laxative suppository, bisacodyl, proved effective in 79.7 per cent while glycerin suppositories were effective in 42 per

Contents continued on page 11



Esidrix potentiates the action of Apresoline, producing good blood pressure response with low dosage, minimal side effects. Added benefits: Improves renal blood flow; relaxes cerebral vascular tone; provides diuresis in decompensated cases. Each combination tablet contains 25 mg. Apresoline and 15 mg. Esidrix.

APRESOLINE® hydrochloride—ESIDRIX® (hydralazine hydrochloride and hydrochlorothiazide CIBA)

CIBA
SUMMIT · NEW JERSEY

2/2762 MB

cent of 109 trials in twenty constipated patients with acute myocardial infarction. Bisacodyl induces peristalsis by specific reflex stimulation of the parasympathetic nerves of the colon. It acts directly on the colonic mucosa and does not depend on systemic absorption for its effect.

Diagnostic Shelf

Relative vs. Organic Mitral Insufficiency . A. A. LUISADA AND J. SZATKOWSKI 111

In a patient considered to have organic mitral insufficiency, left atrial catheterization revealed a pattern of pressure pulse which seemed to confirm the diagnosis. Later, autopsy revealed a normal mitral valve and a recent myocardial infarct. The left atrial pulse was caused by relative mitral insufficiency.

Case Reports

Precipitation of Myocardial Infarction by Postural Hypotension . . FRITZ MAINZER 113

Postural hypotension is suggested as a new factor capable of precipitating myocardial infarction in patients with pre-existing coronary disease. The author describes three elderly patients with postural hypotension in whom myocardial infarction developed upon arising from bed after a moderate period of of bedrest. In one patient the hypotension was apparently increased by the suction effect of the blood due to the sudden release of abdominal pressure by the evacuation of an enema.

Localized Pulmonary Fluid Collections in Congestive Failure Simulating Tumors. Phantom Tumors of the Lung . . . . ISIDORE STEIN AND JOSEPH WEINSTEIN 117

Differentiation of localized pulmonary fluid collections from pulmonary tuberculosis, pneumonia, neoplasm or lung infarction in patients with congestive heart failure is vital to avoid unnecessary thoracic surgery. Characteristically these phantom tumors produce x-ray shadows on the right side between the upper and middle lobes, occasionally in the oblique interlobar fissure. The diagnosis should be suspected when heart enlargement and pulmonary congestion are present, and can be established by using cardiotonic drugs, especially diuretics, which should improve or cure these localized pulmonary collections of fluid if cardiac failure is responsible.

Extreme Hypertrophy of the Left Atrial Appendage. The Case of the Giant Dog Ear EDMUNDS GREY DIMOND, C. FREDERICK KITTLE AND DOUGLAS W. VOTH 122

The unusual case of the giant dog ear is believed to be the first reported occurrence of a hypertrophied left atrial appendage herniated through a pericardial defect, visualized by angiocardiography and corrected by resection. Although the correct diagnosis was first made at surgery, hindsight, equally as important as foresight, enables the authors to attribute the electrocardiographic abnormalities of the P wave and P-R interval in leads III, aVL and aVF to the electrical activity of the hypertrophied left atrial appendage.

Primary Mesothelioma of the Pericardium JEAN L. FOREST AND MICHAEL C. KOZONIS 126

This case of primary mesothelioma of the pericardium is the thirtieth case of primary pericardial tumor reported in the literature. The predominant features were right-sided heart failure, bizarre cardiac enlargement and symptoms of coronary occlusion. In view of the benefits of cardiac surgery, the possibility of an antemortem diagnosis is stressed.

Special Departments

Progress Notes in Cardiology 130
Book Reviews. 132
College News. 133
Announcements 134

Index to Advertisers on page 58

announcing

the keystone in a new and

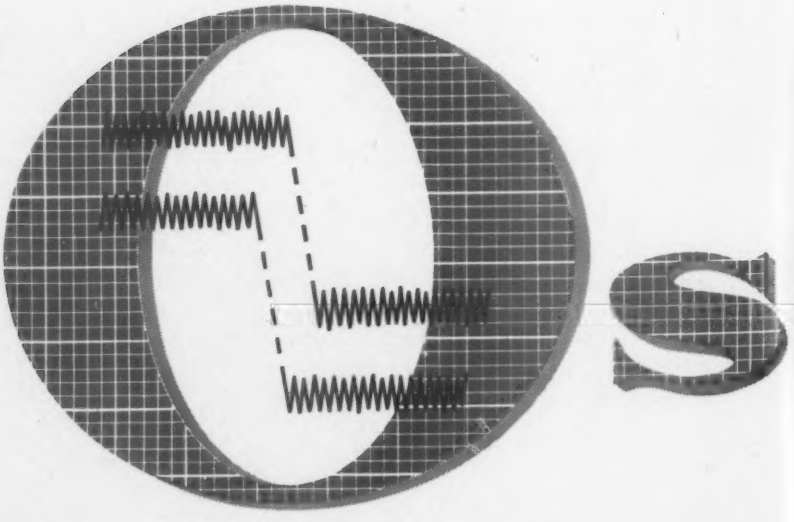
OSTENSIN is a new oral ganglionic-blocking agent of significance to every physician who treats hypertensive patients. The sympathetic blockade produced with OSTENSIN lowers systolic and diastolic blood pressure with predictable effectiveness and yet—because of minimal parasympathetic action—with fewer and less severe by-effects.[1,2,3] OSTENSIN offers further advantages in oral administration, low dosage, smooth and prolonged antihypertensive action, prompt onset, no evidence of inherent toxicity, and rare drug tolerance.[3]

OSTENSIN, used with chlorothiazide or its derivatives, provides a superior new antihypertensive regimen[1,2,3,4] with reduced dosage, by-effects further decreased, and maximal clinical benefits.

OSTENSIN is indicated in diastolic hypertension. (Diastolic hypertension is defined as "... the elevation of diastolic blood pressure to 90 mm. Hg or above."[5])

COMPREHENSIVE LITERATURE SUPPLIED ON REQUEST

TABLETS



Wyeth®
Philadelphia 1, Pa.

OSTENSIN is the registered trademark for Trimethidinium Methosulfate, Wyeth.

effective antihypertensive regimen

BY-EFFECTS OF THREE OTHER GANGLIONIC-BLOCKING AGENTS[6,7,8] COMPARED WITH THOSE OF OSTENSIN[1,9]

	Other Agents	OSTENSIN
Constipation	59-69% of patients	5% of patients
Postural hypotension	33-59% of patients	37% of patients
Visual disturbances	42-50% of patients	34% of patients
Dry mouth	38-41% of patients	15% of patients

"Of particular interest has been the virtual absence of constipation despite adequate blood pressure control. This finding suggests a lower risk of paralytic ileus. . . ."[1]

Supplied: Tablets, scored, 20 and 40 mg., vials of 100.

1. Dunsmore, R.A., et al.: Am. J. M. Sc. *236*:483 (Oct.) 1958. 2. Blaquier, P., et al.: Univ. Michigan M. Bull. *24*:409 (Oct.) 1958. 3. Smirk, F.H.: Submitted for publication. 4. Janney, J.F.: Submitted for publication. 5. Council on Drugs, A.M.A.: J.A.M.A. *166*:640 (Feb. 8) 1958. 6. Freis, E.D., and Wilson, I.M.: Circulation *13*:856 (June) 1956. 7. Moyer, J.H., et al.: A.M.A. Arch. Int. Med. *98*:187 (Aug.) 1956. 8. Moyer, J.H., et al.: Am. Pract. & Dig. Treat. *7*:1765 (Nov.) 1956. 9. Dunsmore, R.A. In Tislow, R.F., et al.: Scientific Exhibit. Presented at Annual Convention of A.M.A., San Francisco, June 23-27, 1958.

tensin®

Ganglionic blockade with fewer and milder by-effects

Your angina patient hardly knows where one leaves off and the other begins. What he does recognize is the relief he gets from **both** when you prescribe CARTRAX.

FOR ANGINAL PAIN

effective drug currently available for prolonged prophylactic

PETN (pentaerythritol tetranitrate) is ". . . the most treatment of angina pectoris."[1]

FOR CARDIAC PANIC

CARTRAX®

PETN + ATARAX®*

"I favor ATARAX [as the tranquilizer for the anxious cardiac] . . . because there is an absence of side effects with this drug, and also because in cardiacs who are troubled with ectopic beats, ATARAX has a quinidine-like action."[2]

Dosage: Begin with 1 to 2 yellow CARTRAX "10" tablets (10 mg. PETN plus 10 mg. ATARAX) 3 to 4 times daily. When indicated, this may be increased by switching to pink CARTRAX "20" tablets (20 mg. PETN plus 10 mg. ATARAX). For convenience, write "CARTRAX 10" or "CARTRAX 20." **Supplied:** In bottles of 100. Prescription only.

*brand of hydroxyzine

References: 1. Russek, H. I.: Postgrad. Med. 19:562 (June) 1956. 2. Russek, H. I.: Presented at the Symposium on the Management of Cardiovascular Problems of the Aged, Dade County Medical Association, Miami Beach, April 12, 1958.

New York 17, N. Y.
Division, Chas. Pfizer & Co., Inc.
Science for the World's Well-Being

Completely reedited, reset in new type, and brought up to date!

PATHOLOGY OF THE HEART

Second Edition

Edited

by

S. E. GOULD, M.D., D.Sc.

Professor of Pathology, Wayne State University
Professor of Pathology, University of Detroit School of Dentistry
Detroit, Michigan
Director of Pathology, Wayne County General Hospital
Eloise, Michigan

With a Foreword by

HOWARD T. KARSNER, M.D.

Five outstanding new chapters have been added . . .

- **The conduction system**
- **Cardiopulmonary disease**
- **Diseases of the aorta**
- **Surgery of the heart**
- **Histochemical study of the heart**

All chapters prepared **by recognized authorities in the field.** A correlation of the pathologic with the clinical makes this an eminently practical work. Extensive indices of authors and subjects enable the reader to locate answers quickly and easily.

SURPASSING IN SCOPE THE HIGHLY PRAISED FIRST EDITION

"The editor and authors should be congratulated on a superb contribution. The book is a 'must' for every pathologist and cardiologist and can be usefully consulted by every physician."—*A.M.A. ARCHIVES OF PATHOLOGY*

". . . . highly recommended for cardiologists and pathologists and others interested in obtaining the 'last word' on any pathologic aspect related to diseases of the heart."—*HAWAII MEDICAL JOURNAL*

"The outstanding work that may result when a group of able men pool their knowledge to produce a comprehensive discussion of a subject is admirably exemplified by PATHOLOGY OF THE HEART."—*THE UNITED STATES QUARTERLY BOOK REVIEW*

". . . an excellent source of factual material for any cardiac study."—*GP*

1152 pages 977 illustrations (6 color plates)

Publication date December 1959
$32.50

20 DISTINGUISHED CONTRIBUTORS

Archie H. Baggenstoss
Charles P. Bailey
Alexander Barry
Jesse E. Edwards
Ira Gore
S. E. Gould
Harold D. Green
Miguel A. Guerrero
Willard T. Hill
Joseph E. Imbriglia
Edward B. Krumbhaar
Maurice Lev
Averill A. Liebow
Joseph F. A. McManus
Alan R. Moritz
Gordon B. Myers
Bradley M. Patten
Otto Saphir
Walter A. Stryker
William B. Wartman

CHARLES C THOMAS • PUBLISHER 301-327 East Lawrence Avenue SPRINGFIELD • ILLINOIS

90% of anxious, agitated

and apathetic office patients

calmed *without* drowsiness

and with normal drive restored . . .

on one or two 0.25 mg. tablets b.i.d.:

This is the pattern of performance for

PERMITIL®

Fluphenazine dihydrochloride

In Anxiety and Anxiety-induced Depression

"In contrast to other phenothiazines, it [PERMITIL] mitigates apathy, indifference, inertia and anxiety-induced fatigue. Thus, instead of impeding effective performance of daily tasks, it increases efficiency by facilitating psychic relaxation. Consequently, acceptance of this drug, especially by office patients, has been excellent."[1]

- In 608 patients with anxiety and anxiety-induced fatigue or depression, PERMITIL, administered in small daily doses of 0.5 mg. to 1 mg., produced significant improvement in 90%.[2]
- PERMITIL is virtually free from side effects at recommended dosage levels.
- Patients become calm without being drowsy and normal drive is restored.
- Onset of action is rapid; effect is prolonged.
- PERMITIL does not potentiate barbiturates or non-barbiturate sedatives and can be used with impunity with such agents.

How to prescribe PERMITIL: The lowest dose of PERMITIL that will produce the desired clinical effect should be used. The recommended dose for most adults is one 0.25 mg. tablet twice a day (taken morning and afternoon). Increase to two 0.25 mg. tablets twice a day if required. Total daily dosage in excess of 1 mg. should be employed only in patients with relatively severe symptoms which are uncontrolled at lower dosage. In such patients, the total daily dose may be increased to a maximum of 2 mg., given in divided amounts. Complete information concerning the use of PERMITIL is available on request.

SUPPLIED: Tablets, 0.25 mg., bottles of 50 and 500.

REFERENCES: 1. Ayd, F. J., Jr.: Current Therapeutic Research 1:41 (Oct.) 1959. 2. Recent compilation of case reports received by the Medical Department, White Laboratories, Inc.

PERMITIL

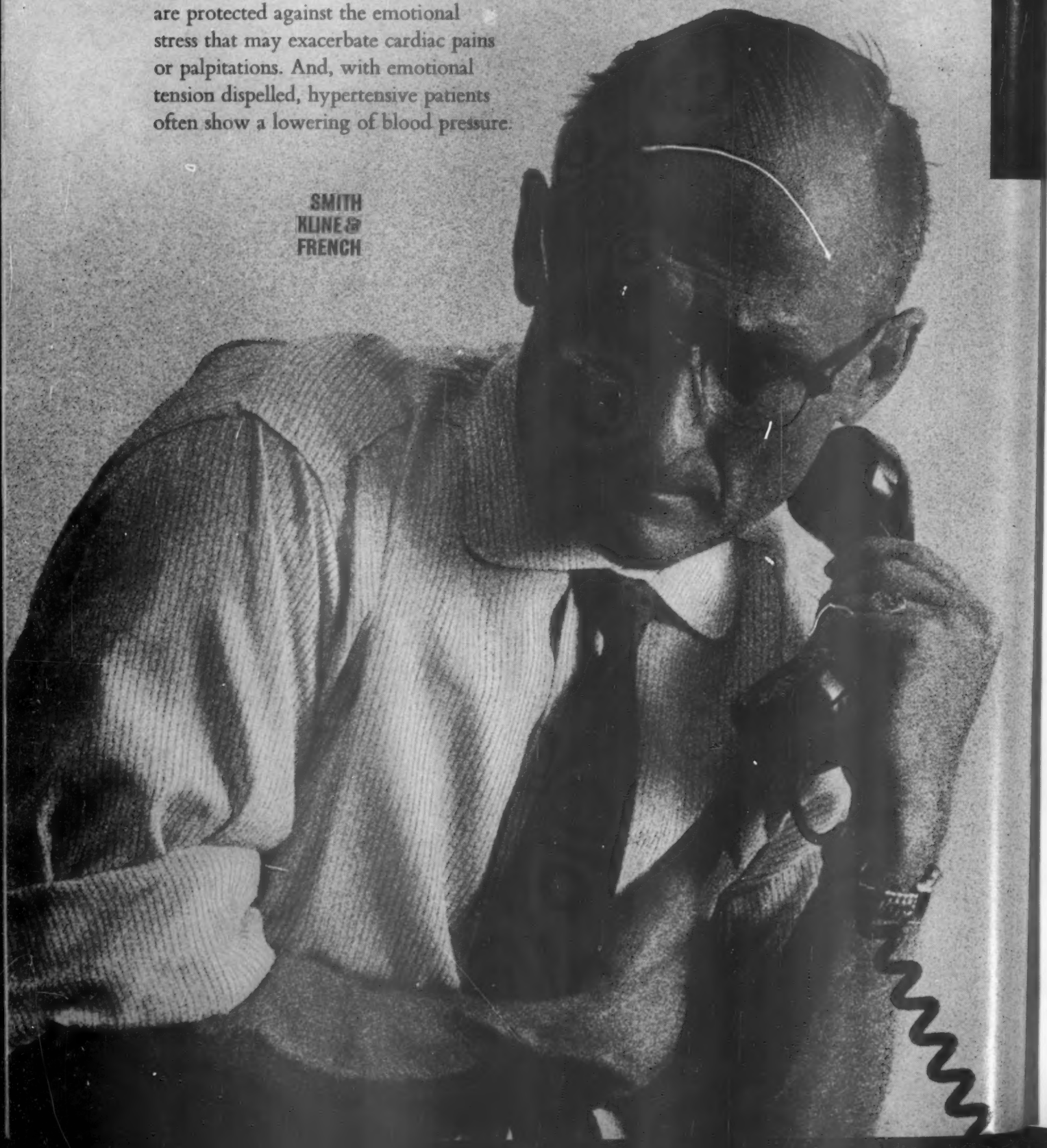
White WHITE LABORATORIES, INC., KENILWORTH, NEW JERSEY

in cardiac patients · Compazine®

brand of prochlorperazine

reduces the impact of emotional stress—
relieves fear and apprehension.
On 'Compazine', many "heart worriers"
are protected against the emotional
stress that may exacerbate cardiac pains
or palpitations. And, with emotional
tension dispelled, hypertensive patients
often show a lowering of blood pressure.

SMITH
KLINE &
FRENCH



INTRODUCING

ISORDIL

a new
coronary vasodilator
of
unprecedented effectiveness
for
angina pectoris

1 **rapid onset**

2 **prolonged action**

3 **consistent effect**

4 **unusual safety**

ISORDIL significantly reduces the number, duration, and severity of anginal attacks, often when other long-acting coronary vasodilators fail. Exercise tolerance is increased, pain decreased, and the requirements for nitroglycerin either drastically curtailed or eliminated.

ISORDIL acts rapidly in comparison with other prophylactic agents, and patients usually experience benefits within 15 to 30 minutes. The effects of a single dose of ISORDIL persist for 4 to 5 hours. Thus, for most patients, convenient q.i.d. administration is highly satisfactory.

The only side effect observed has been transitory, easily controlled headache, normally considered an expression of effective pharmacodynamic activity.[1] The toxicity of ISORDIL is extremely low, approximately 50 times the therapeutic dose being required to produce toxic symptoms.

Sherber,[2] summarizing his experience with ISORDIL, states it is "the most effective medication for the treatment of coronary insufficiency available today."

ISOR

Isos

IVES*

IVES-CAMERON COMPANY • New York 16, New York

Clinical and Laboratory Data Confirm Superiority

Succeeds where others fail:

Among 48 patients[3] previously treated with other coronary vasodilators, chiefly pentaerythritol tetranitrate, ISORDIL was demonstrably superior in 37, equivalent in 9, and inferior in 2. Response of patients treated in all studies[4] was 85% good, 7% fair, and 8% poor.

Markedly reduces number of anginal attacks:

Albert[5] found that of 29 patients receiving ISORDIL, 25 responded well, 1 moderately well, and 1 not at all. Effectiveness could not be judged in 2 patients. For those who responded well, the frequency of anginal attacks was quickly reduced from a daily average of 5 to 1.2. Continued use of ISORDIL further reduced the frequency of attacks.

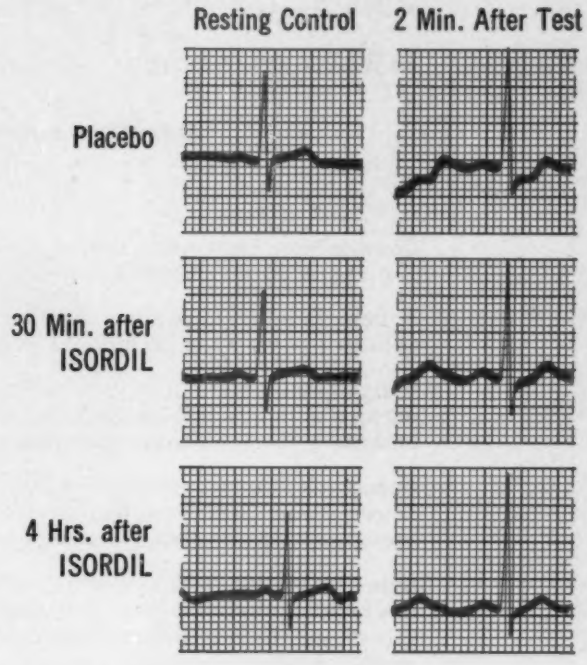
Increases tolerance to exercise and stress:

Electrocardiographic response following the Master two-step test has clearly established a more favorable balance between oxygen supply and demand to the myocardium with ISORDIL therapy. Eight of 10 patients administered ISORDIL in studies by Russek[6] showed considerably less abnormality in the post-exercise electrocardiogram than before treatment.

Rapid onset and prolonged action a function of solubility and metabolism:

Pharmacologic studies indicate that the rapid onset and prolonged action shown by ISORDIL are related to its high solubility and low rate of metabolism.[7] Incubation with liver slices suggest rapid absorption and delayed inactivation by the liver.

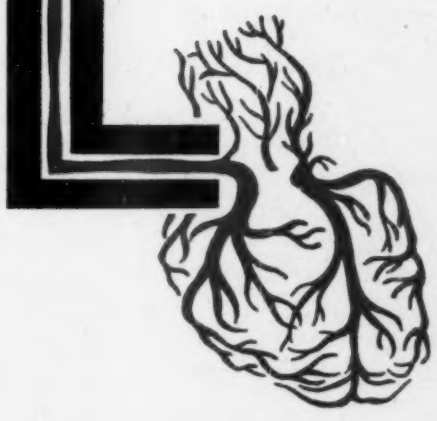
Master Test Responses (Lead V_4) in a 58-Year-Old Male with Angina Pectoris[6]



unprecedented effectiveness in angina pectoris

ISORDIL*

Isosorbide Dinitrate, Ives-Cameron



*Trademark

- **NEW—for more effective control of angina pectoris**
- **Reduces number, duration, and severity of anginal attacks**

"Isordil is a new and effective agent for therapy of angina pectoris."—Russek[6]

Composition: Each white, scored tablet of ISORDIL (Isosorbide Dinitrate) contains 10 mg. of 1,4,3,6-dianhydro-sorbitol-2,5-dinitrate.

Action: Following oral administration of ISORDIL, the effects of coronary vasodilatation are apparent within 15 to 30 minutes and persist for 4 to 5 hours.

Indications: ISORDIL is indicated for the therapeutic and prophylactic management of angina pectoris and coronary insufficiency. It is often useful in patients only partially responsive to other long-acting coronary vasodilators.

Dosage: ISORDIL is administered orally. Average dose is one tablet (10 mg.) taken one half hour before meals and at bedtime. Individualization of dosage may be necessary for optimum therapeutic effect; dosage may vary from 5 mg. to 20 mg. q.i.d.

Side Effects: Side effects are few, infrequent, and mild. Transitory headache, common to effective nitrate or nitrite therapy, has occurred. This usually responds to administration of acetylsalicylic acid, and disappears with continued therapy. When headache is persistent, reduction in dosage may be required.

Caution: ISORDIL should be given with caution in patients with glaucoma.

Supplied: Bottles of 100.

References: 1. Riseman, J.E.F., et al.: Circulation **17**:22-39 (Jan.) 1958. 2. Sherber, D.A.: Personal Communication (Oct., 1959). 3. Case Reports on File, Ives-Cameron Company (1958-1959). 4. Summary of Case Reports on File, Ives-Cameron Company (1958-1959). 5. Albert, A.: Personal Communication (Oct., 1959). 6. Russek, H.I.: Personal Communication (Oct., 1959). 7. Harris, E., et al.: Personal Communication (Oct., 1959).

ISORDIL

IVES

IVES-CAMERON COMPANY • New York 16, New York

PROVEN EFFECTIVE FOR THE TENSE AND NERVOUS PATIENT

"There is perhaps no other drug introduced in recent years which has had such a broad spectrum of clinical application as has meprobamate.* As a tranquilizer, without an autonomic component in its action, and with a minimum of side effects, meprobamate has met a clinical need in anxiety states and many organic diseases with a tension component."

Krantz, J. C., Jr.: The restless patient—A psychologic and pharmacologic viewpoint. Current M. Digest 25:68, Feb. 1958.

***Miltown®**

the original meprobamate, discovered and introduced by

WALLACE LABORATORIES, *New Brunswick, N. J.*

CM-213

Originators and Sole Producers of a complete line of

★ **Cardiac Catheters and Electrodes**

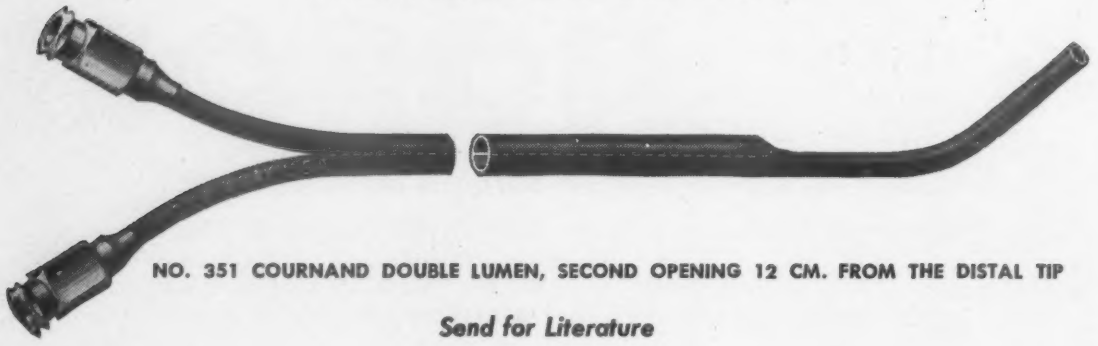
★ **Edwards' Knitted and Woven Arterial Grafts and Bifurcations of Teflon®**

★ **Detergicide, for Cleaning and Disinfecting; Available as a Concentrated Solution**

Developed and approved in cooperation with the Medical Profession

A Research and Experimental Department is Maintained for the development of Cardiac Instruments and Teflon Vascular Prostheses in collaboration with the Medical Profession.

NO. 350 COURNAND SINGLE LUMEN CATHETER



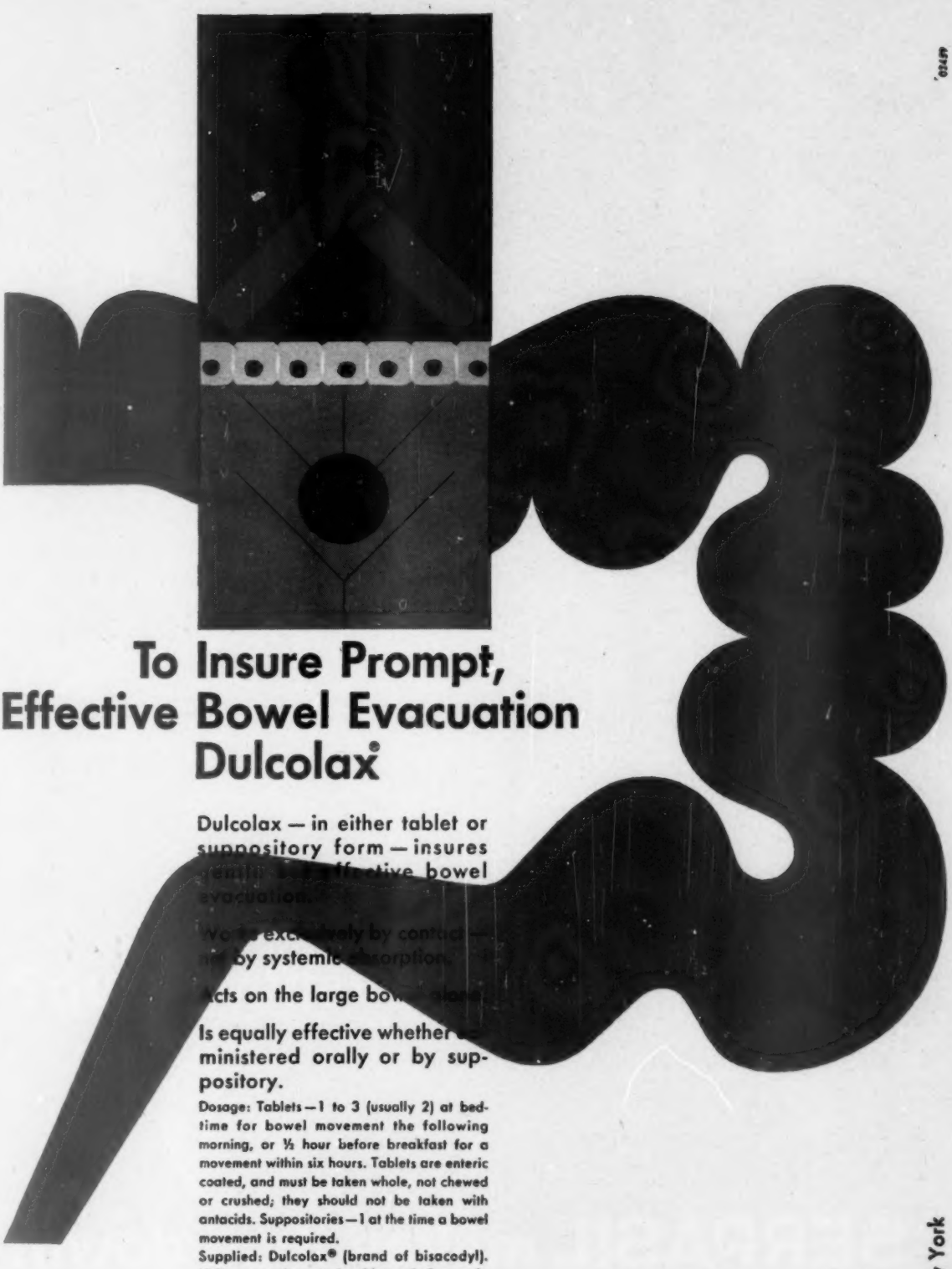
NO. 351 COURNAND DOUBLE LUMEN, SECOND OPENING 12 CM. FROM THE DISTAL TIP

Send for Literature

United States Catheter & Instrument Corp.

Glens Falls, New York

® Teflon is the trade name of E. I. du Pont de Nemours & Co., Inc., for its tetrafluorethylene resin and fiber.



To Insure Prompt, Effective Bowel Evacuation Dulcolax®

Dulcolax — in either tablet or suppository form — insures prompt, safe, effective bowel evacuation.

Works exclusively by contact — not by systemic absorption.

Acts on the large bowel alone.

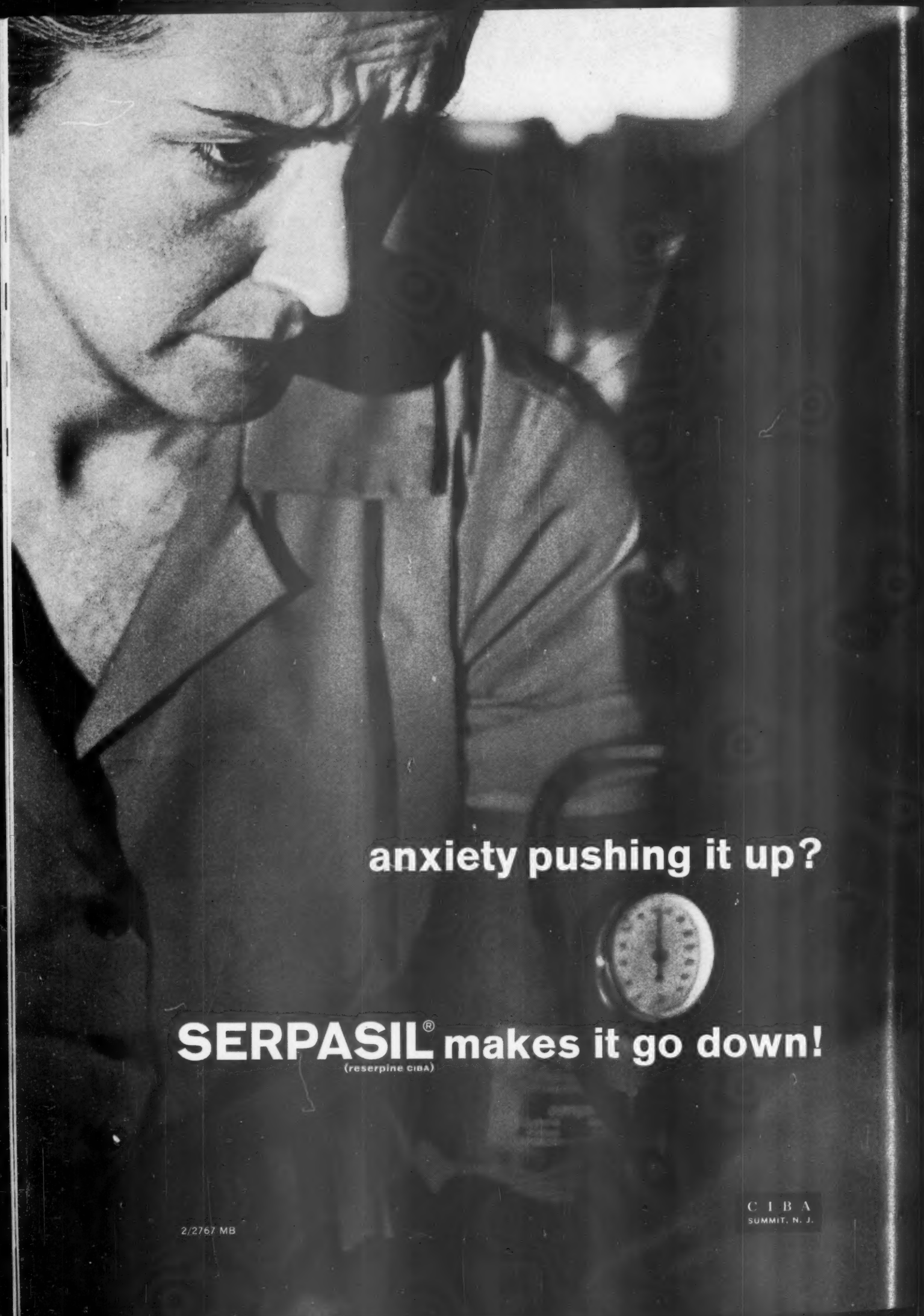
Is equally effective whether administered orally or by suppository.

Dosage: Tablets—1 to 3 (usually 2) at bedtime for bowel movement the following morning, or ½ hour before breakfast for a movement within six hours. Tablets are enteric coated, and must be taken whole, not chewed or crushed; they should not be taken with antacids. Suppositories—1 at the time a bowel movement is required.

Supplied: Dulcolax® (brand of bisacodyl). Yellow enteric-coated tablets of 5 mg. in boxes of 6 and bottles of 100. Suppositories of 10 mg. in boxes of 6. Under license from C. H. Boehringer Sohn, Ingelheim.

Contact Laxative

Geigy Ardsley, New York


anxiety pushing it up?
SERPASIL® makes it go down!
(reserpine CIBA)
2/2767 MB
CIBA
SUMMIT, N. J.

in angina pectoris...

24-hour protection against both pain and fear with just one

COROVAS® Tymcap b.i.d.

Clinically proved[1,2,3] to establish peak nitrate blood levels soon after an initial dose and to maintain these levels throughout a 12-hour period...

thus avoiding bothersome t.i.d. or q.i.d. routines, yet permitting the patient to enjoy up to 12 hours' uninterrupted relief from pain and fear with a single COROVAS Tymcap: "...it would appear that 60 mg. of PETN in TD capsule form [timed-disintegration COROVAS Tymcaps] is as effective as 80 mg. PETN in tablet form, in controlling the anginal attacks."[3]

COROVAS Tymcaps

prolonged, sustained-action of vasodilating pentaerythritol tetranitrate (PETN) 30 mg., and sedative secobarbituric acid 50 mg.

- *controls or prevents anginal pain*
- *alleviates associated fear, apprehension and panic*
- *reduces frequency and severity of attacks*
- *reduces the need for nitroglycerin*

Supplied—Boxes of 60 and 120

1. Feinblatt, T. M., and Ferguson, E. A.: New Eng. J. Med. 256:331 (Feb.) 1957.
2. Kupersmith, I. H.: International Record of Medicine, Vol. 171 No. 10 (Oct.) 1958.
3. Berry, J. W., and Roach, T. C.: Circulation, Vol. 17, No. 6 (June) 1958.

Amfre-Grant Inc. Brooklyn 26, New York

ARE YOU ACHIEVING TRUE COLD STERILIZATION?

WAREXIN*

IS LETHAL TO—*FUNGI, BACTERIA, VIRUSES, RESISTANT SPORES*—IN LESS THAN 1 HOUR—AND YET IS NON-TOXIC!

*WAREXIN: Clorpactin (a group of hypochlorous derivatives) to which buffers have been added for stability.

PREVENT CROSS-INFECTION!

Sterilize with **WAREXIN**

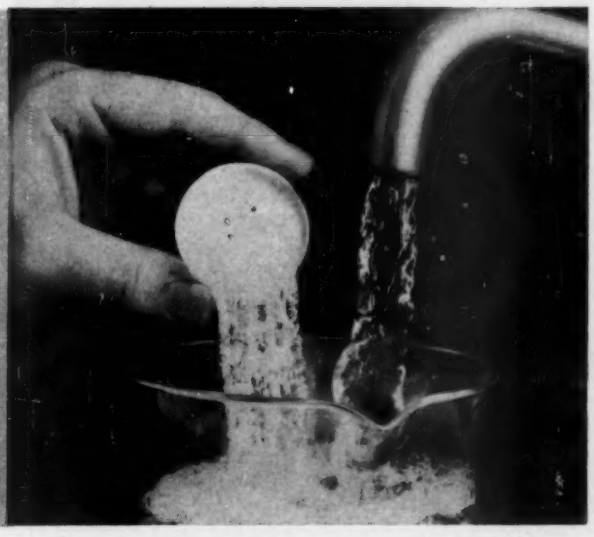
Can safely be used for:

1. All instruments made of stainless steel or other widely used corrosion-resistant alloys—even fine stainless hypodermic needles.
2. Articles made of rubber, plastic, non-porous fibers, glass, porcelain, enamel.
3. Complex equipment such as anaesthesia apparatus, heart-lung machines, artificial kidneys, etc.
4. Containers such as colostomy bags, urinals, air filters.
5. Special surfaces: hospital and laboratory walls, floors, tables.

MIX WITH ORDINARY TAP WATER

Because Warexin concentrate is a *true* Cold Sterilizing Agent, it is unnecessary to use distilled water. Just add 1 level measure to each quart of tap water. Warexin solution gives you effective kill in 1 hour or less.

ECONOMICAL! A 5 oz. bottle makes 12-16 quarts of solution. Cost: approximately 27¢ a quart!



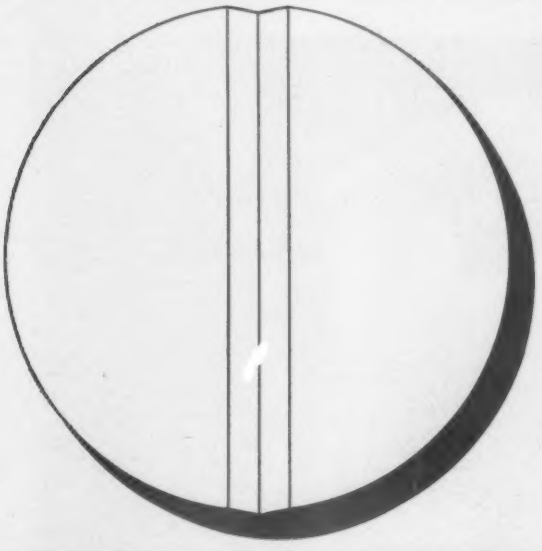
DAVOL RUBBER COMPANY
PROVIDENCE 2, R. I.

Lattimer, John K., and Spirito, A. L.: Clorpactin for Tuberculosis cystitis: Instrument sterilization, *Journ. of Urology*, Vol. 73, No. 6, June, 1955. • Wolinsky, E., Smith, M. M. and Steenken, Wm. Jr., Tuberculocidal Activity of Clorpactin. A New Chlorine Compound, *Antibiotic Medicine*, 1:382-384, July, 1955. • Sanders, Murray and Soret, M. G.: Virucidal activity of WCS-90, *Antibiotics and Chemotherapy*, Vol. V, No. 11, Nov. 1955. • Gliedman, M. L., Lt. (MC) USNR, Grant, R. N. Capt. (MC) USN, Vestal, B.L., B.S., and Karlson, K.-E., M.D.; Impromptu Bowel Cleansing and Sterilization, *Surgery*, 43:282-287. • From The Textbook, Extracorporeal Circulation, Edited by Dr. J. Garrott Allen, Page 87; Charles C. Thomas, Publisher.

GREATER CONVENIENCE

DOUBLE POTENCY

AT LOW COST TO YOUR PATIENT



Pentids '400'

Squibb 400,000 units Buffered Penicillin G Potassium Tablets

For the treatment of penicillin susceptible infections—ranging from **mild to moderately severe**—due to **hemolytic streptococcus / pneumococcus / staphylococcus / and for the prevention of streptococcal infections where there is a history of rheumatic fever**

Clinical effectiveness confirmed by millions of cases
Specific in many common infections
Daily dosage may be spaced without regard to mealtime
Ease of administration with oral penicillin
Economy for the patient

SQUIBB

Squibb Quality—the Priceless Ingredient

new convenient oral tablets

PENTIDS '400,' each scored tablet contains 400,000 units of penicillin G potassium buffered, bottles of 12 and 100. Twice the unitage of Pentids 200,000 units.

PENTIDS® IS A SQUIBB TRADEMARK

also available

PENTIDS, 200,000 units of buffered penicillin G potassium per scored tablet, bottles of 12, 100, and 500.

PENTIDS FOR SYRUP, 200,000 units of penicillin G potassium per teaspoonful (5 cc.), 12 dose bottles.

PENTIDS, CAPSULES, 200,000 units of penicillin G potassium per capsule, bottles of 24, 100, and 500.

PENTIDS SOLUBLE TABLETS, 200,000 units of penicillin G potassium per tablet, vials of 12 and bottles of 100.

PENTIDS-SULFAS TABLETS, 200,000 units of penicillin G potassium with 0.5 Gm. triple sulfas per tablet, bottles of 30, 100, and 500.

a refinement in rauwolfia alkaloid therapy

moderil®

brand of rescinnamine

for better management of hypertension

a purified alkaloid of rauwolfia . . . lessens the frequency and/or severity of these reserpine side effects:

mental depression • bradycardia • sedation • weakness • fatigue • lassitude • sleepiness • nightmares • gastrointestinal effects

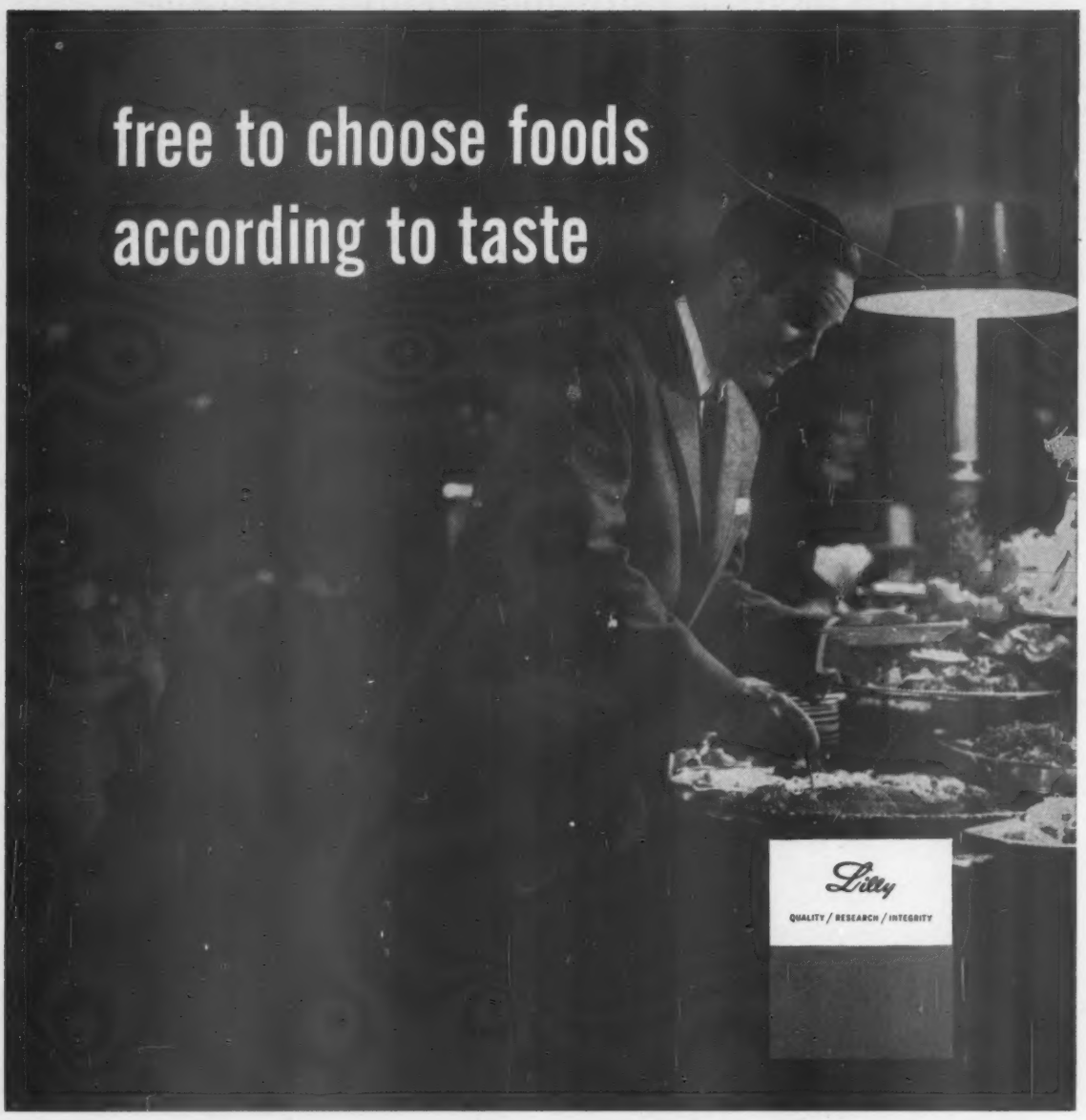
useful *alone* for gradual, sustained lowering of blood pressure in mild to moderate labile hypertension

useful *as an adjunct* to other antihypertensive agents, permitting their use in lower, better tolerated dosage

Professional information available on request

PFIZER LABORATORIES Division, Chas. Pfizer & Co. Inc., Brooklyn 6 N.Y.

Pfizer *Science for the world's well-being™*



CYTELLIN® lowers elevated serum cholesterol without severe dietary restrictions

Cytellin is the only product that literally prevents cholesterol from entering the circulation. It reduces absorption of both dietary and endogenous cholesterol by uniting with it and rendering it virtually insoluble in the G.-I. tract. Thus, cholesterol is "tied up" and ultimately eliminated.

In at least 85 percent of cases, Cytellin taken just before each meal will permit patients to eat a satisfying, normal diet. There are no contraindications, toxic manifestations, or side-effects to Cytellin.

Cytellin® (sitosterols, Lilly)

ELI LILLY AND COMPANY • INDIANAPOLIS 6, INDIANA, U.S.A.

973000

The American Journal of Cardiology

VOLUME V JANUARY 1960 NUMBER 1

EDITORIAL

Surgical Treatment of Angina

THE accounts of angina pectoris, from Heberden to Herrick, noted that while sudden death was often the outcome, many patients carried out active professional and recreational programs over years or decades, and some patients "outgrew" the disease in months or years. Refractory, intractable, disabling angina has always been a minority problem, more frequent in aortic than in coronary cases.

Operations to Sever Nerve Pathways: Following World War I, attack on these cases by surgical section of nerves proved extremely effective. Resection of the left superior cervical sympathetic ganglion (Coffey-Brown[1]) or of the so-called "depressor nerve" (Hofer[2]) proved almost as successful as resection of the left stellate ganglion or the upper sympathetic dorsal branches. The latter operations severed the pain pathways, and it was feared this might hasten sudden death by removing the "danger signal." Actually, survival of patients with severe angina after these operations was longer than that of control subjects with less severe disease.[3] Acute bouts of pain are reminders of the risk of death, and the relief from this reduces the stress of constant dread, far worse than any of the socioeconomic stresses which appear to hasten onset of coronary obstruction.

While the stellate resections and dorsal sympathectomy "cure" practically all cases of aortic or coronary angina, the other operations on nerves, which do not touch pain fibers, cure over 50 per cent. So does thyroidectomy, even before the metabolism falls. Powdering the pericardial sac, implanting omentum, pectoral muscles, or mammary arteries, and even ligating mammary arteries also cure more than half the anginal subjects before any collateral could possibly develop. Thus any operation which the surgeon and patient believe a cure for angina has a striking effect in most subjects. During the twenties and thirties of this century, physicians who believed in focal infection "cured" many cases of angina by having teeth extracted or gallbladders removed.

Coronary Endarterectomy: With recent progress in endarterectomy and arterial replacement for ischemia of the legs, brain and kidneys it was inevitable that similar technics would be applied to the coronary arteries. The recent report of Longmire, Cannon and Kattus,[4] and the symposium in which these workers were joined by Blumgart and Bailey,[5] prove that this is the right path, although a steep and hazardous one. The risk of death during operation can be reduced by artificial "hearts," no artificial "lungs" being needed, and perhaps by cooling. The great risk of recurrence of thrombosis in the endarterectomized vessel, with its lining of raw fibroblasts, can be reduced by heparin therapy, and perhaps by the use of fibrinolysins, during the first few weeks after operation. The risk of rapid atheroma formation in abnormally lined vessels, so apparent in the syphilitic aorta, can be reduced by meticulous dietary control and use of nicotinic acid by patients who have undergone this operation.

Indications for Endarterectomy: It is not likely that this procedure will be used for those who have healed infarction without angina, or for those who have heart failure after infarction. Coronary angiography is not yet sufficiently safe and sharp for making possible definition of anatomic situations in which collateral circulation around narrow points in the coronary lumen is adequate to prevent necrosis while such a point is surgically repaired. Thus intervention now must be limited to those with angina who have widespread and marked S-T segment depression during attacks, with no evidence of local S-T segment elevation and QRS alteration. The latter changes point to local ischemia with

inadequate collateral, the former to obstruction of main channels with abundant collateral. The experience both of pathologists and of surgeons shows that most patients with angina have complete obstruction of two of the three main arteries, and all have at least one major vessel closed. They must have abundant collateral and diffuse ischemia must occur on effort. These vessels may have very short (<1 cm.) occlusions, or be occluded for as much as 8 cm. During endarterectomy, there need be no local ischemia, as there would be in operations on partially occluded vessels.

While preoperative and postoperative coronary angiography is often most informative, it is not essential; poor visualization may be misleading. What is essential is clear-cut and striking S-T depression evoked by modest exertion before operation, and normal tracings on vigorous exertion after operation. Subjective cure and even prolonged life in angina is of no value as evidence of effective restoration of coronary flow.

Surgical intervention for mild angina, with no striking electrocardiographic change on exertion, cannot be justified now. It might lead to infarction if a partially occluded vessel is blocked during endarterectomy. Definitive cure of coronary obstruction with angina is a fact, but this is no place for the beginner, either in medicine or surgery. Careful study, meticulous surgery, and sound postoperative prophylaxis of atherosclerosis will give maximal benefit with minimal risk.

WILLIAM DOCK, M.D.
State University of New York
Brooklyn, New York

REFERENCES

1. BROWN, P. K. and COFFEY, W. B. Surgical treatment of angina pectoris. *Arch. Int. Med.*, 34: 417, 1924.
2. WENCKEBACH, K. F. Angina pectoris and possibilities for its surgical relief. *Brit. M. J.*, 1: 809, 1924.
3. WHITE, J. C. and BLAND, E. F. The surgical relief of severe angina pectoris. *Medicine*, 27: 1, 1948.
4. LONGMIRE, W. P., JR., CANNON, J. A. and KATTUS, A. A. Direct vision coronary endarterectomy for angina pectoris. *New England J. Med.*, 259: 993, 1958.
5. BLUMGART, H. L., KATTUS, A. A., LONGMIRE, W. P., JR. and BAILEY, C. P. Symposium on Direct Relief of Coronary Occlusion. Section on Experimental Medicine and Therapeutics, Annual Meeting of A M.A., Atlantic City, June 9, 1959.

Clinical Studies

Thromboendarterectomy for Coronary Artery Disease*

CHARLES P. BAILEY, M.D., F.A.C.C.,† DRYDEN P. MORSE, M.D. *and* WILLIAM M. LEMMON, M.D.†

Philadelphia, Pennsylvania

CORONARY arterial disease, which usually is of atherosclerotic origin, has been indicted as causative of an increasingly large percentage of deaths among Americans, and is a grave problem in many other countries. In 1951, 299,109 deaths in the United States were attributed to this disease or its complications.[1] In 1958 this number had increased to 427,516.[2] It is believed currently that atherosclerotic disease is of metabolic origin, and many think that its development is intimately associated with a deficit in the assimilation and utilization of fats. This, in turn, may be related to the eating and exercise habits consistent with our modern culture and way of life. Such problems are beyond the scope of this paper.

However, many of the effects of well developed atherosclerosis are of a mechanical nature. Hence, it is often logical, in the individual case, to apply appropriate mechanistic therapy. Since surgery is the mechanical arm of therapeutics, surgical intervention, then, becomes conceivable therapy for the atherosclerotic process. This philosophy has achieved widespread acceptance for atherosclerotic disease in some parts of the body, i.e., the aorta,[3,4] the arteries of the extremities[5] and the carotid arteries.[6] It is not inconsistent, therefore, to apply similar thought patterns to treatment of the process as it affects the coronary arteries.

PATHOLOGY

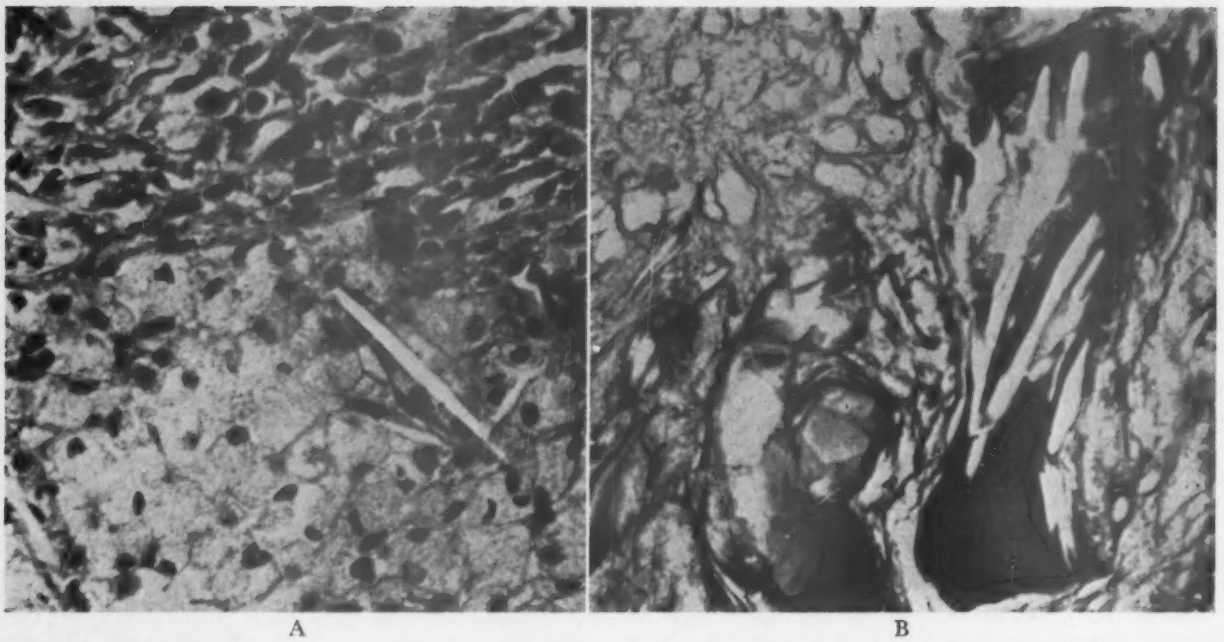
Dock[7] has documented the predilection for atherosclerosis to involve the coronary arteries. In general, coronary atherosclerosis precedes similar involvement of any of the other large or small arteries of the body and in men below the age of forty years it may be the only demonstrable pathologic condition of this type.

The process as it affects the arteries of the heart is, in most respects, similar to that seen in other regions with two very significant differences to be mentioned later. The lesions universally tend to be segmental in distribution and appear first at sites of increased circulatory trauma (such as at a point of bending in the course of a vessel). They consist of macular or maculopapular subintimal depositions of lipid material (cholesterol and cholesterol esters) surrounded by a variable amount of reactive fibrous encapsulation (Fig. 1). In advanced stages the lesions may become confluent. As they enlarge they tend to elevate the intima and endothelial lining of the artery to encroach upon the lumen. Such elevated areas may become "ulcerated" with interruption in the continuity of the endothelial covering. The lipid contents may become discharged into the vascular lumen. Often a thrombus develops on the roughened surface. This may grow sufficiently to occlude the vessel completely, or it may remain as a sessile coating over the lesion. Infrequently sudden hemorrhage within the substance of the atheroma causes a rapid increase in its size which may serve to complete the vascular obstruction.

Differences Between Coronary and Peripheral Atherosclerosis: Subtotal obstruction of a major

* From the Department of Thoracic Surgery, Bailey Thoracic Clinic, the Cardiopulmonary Division, Einstein Medical Center, Department of Thoracic Surgery, Hahnemann Medical College and Hospital, and the Philadelphia General Hospital, Philadelphia, Pennsylvania.

† Present address: New York Medical College, New York, New York.



A B

FIG. 1. A, macrophages in encapsulating zone of infiltration about an atheromatous lesion. B, cholesterol crystals within an atheromatous plaque. (From: FORBUS, W. D. Reaction to Injury, p. 201. Baltimore, 1951. Williams & Wilkins Co.)

nutritional artery to a part tends to cause pain when the circulatory demands exceed the supply as during increased physical exertion. In the case of muscular arteries partial obstruction is often associated with muscular spasms on activity. In the extremities this is termed intermittent claudication. In the heart it is called angina pectoris. Total obstruction also causes pain unless an adequate collateral circulation exists. In its absence actual infarction and necrosis of the ischemic area will ensue. The atherosclerotic process will not infrequently extend to and involve the smallest ramifications of the popliteal and peroneal arterial systems when it affects the lower extremities.

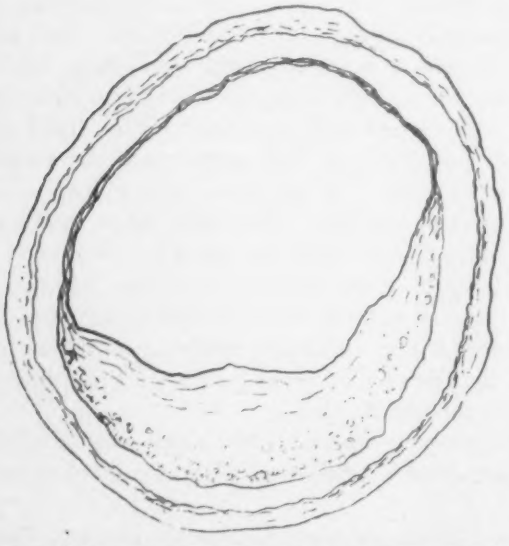


FIG. 2. Atheromatous lesions nearly always appear first upon the myocardial aspect of a coronary artery. Note that they elevate the intima and involve its deeper layers.

One of the two dissimilarities between peripheral and coronary atherosclerosis is the characteristic tendency of the disease to be limited to the visible or epicardial coronary arterial branches when it affects the coronary arteries, and almost never to affect any of the deeper or intramural branches with the single exception of the septal branch of the left coronary artery. Thus, one may expect the minute vascular "run-off" pathways to be open more consistently in coronary arterial disease then in peripheral atherosclerosis. This augers well for the success of direct coronary arterial surgery whether it involves excision of a segment and grafting, bypass anastomosis, or an endarterectomy type of procedure.

Another important clinical difference between coronary arterial disease and peripheral atherosclerosis is that acute arterial occlusion in the former condition may result in the setting up of differences in the electrical potentials of adjacent portions of the myocardium which can lead to the onset of ventricular fibrillation—the "self-electrocution" of Beck.[8] Arterial occlusion in a limb can produce gangrene of tissue, but it never can produce a "mechanism" death.

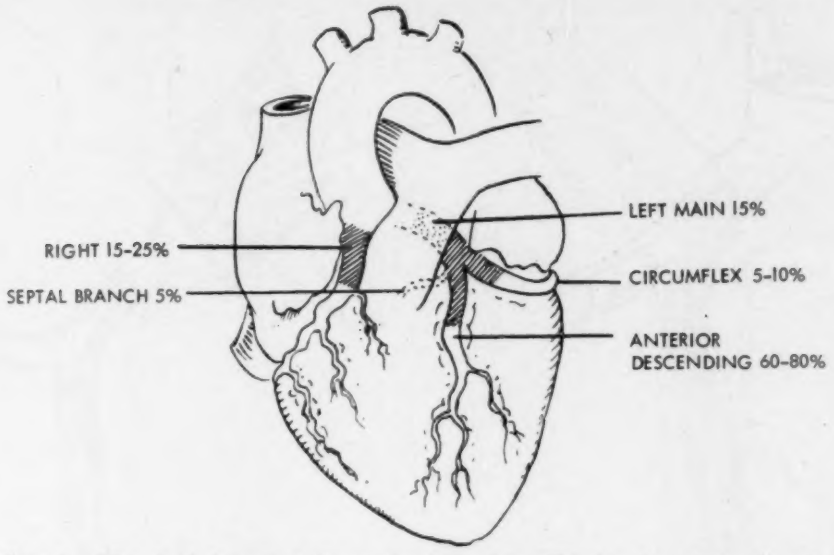


FIG. 3. The shaded areas indicate the sites of predilection for atherosclerotic involvement of the coronary arteries.

The atheromata develop first upon the myocardial wall of the coronary artery but because of the small size of the vessel do not assume a maculopapular distribution. On cross-section the involved segment of the artery appears as a "signet ring" (Fig. 2).

Distribution of Coronary Lesions: The localization of the disease and its pattern of progression are fairly predictable. According to Schlesinger and Zoll[9] the disease usually begins within the first two centimeters of the anterior descending branch of the left coronary artery. The lesion extends in both antegrade and retrograde fashion, thus involving the first portion of the septal branch and also the main left coronary artery. The left circumflex branch often is spared, but sometimes is involved extensively. The right coronary artery is extremely vulnerable, being involved next most commonly after the anterior descending branch.[10] By the time of death from this disease the most extensive changes are seen in the first third of each of these vessels, less involvement being seen in the middle third and least in the distal third (Fig. 3).

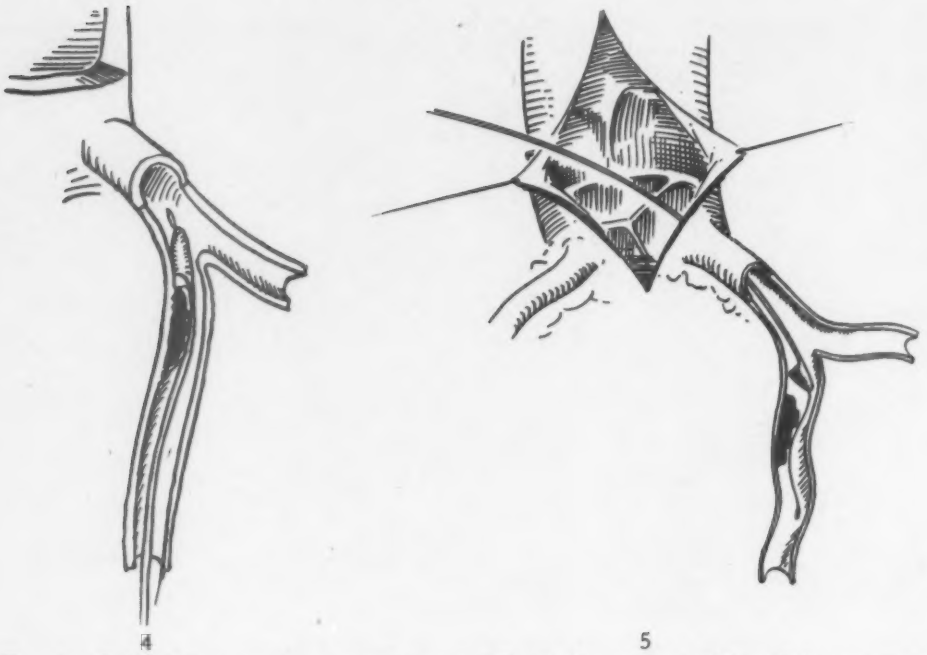
Results of Coronary Obstruction: With sufficiently gradual encroachment upon the lumen of (and hence of flow through) a large coronary artery, the normally present but minute intercoronary arterial collaterals progressively become larger, thus converting the natural end-arterial pattern of the coronary tree to one more "arcuate" in its intimate architecture. Schlesinger, Zoll and Blumgart[11,12] have demonstrated these pathways by injection technics and have described their augmentation experimentally in animals and by the effects of disease in man. The chief stimulus to their development appears to be localized or generalized hypoxia of the myocardium.

In the heart the progressive narrowing of a major coronary artery brings about reduction in the blood flow to the supplied area. At a certain critical point of narrowing (in the absence of an adequate collateral supply) pain described under the term of "angina pectoris" will develop upon increased exertion. This painful sensation may be considered as a prodromal sign, portending the eventual completion of the vascular occlusion.

When coronary occlusion becomes complete in the absence of adequate collateral pathways the ischemic area becomes infarcted. The fate of such an area of necrosis is variable. If death does not take place at once, due either to disruption of the functional integrity of the heart as a pump (in large infarctions) or due to the onset of ventricular fibrillation ("mechanism death"), absorption and healing by fibrosis is the rule. This results in a firm scar of replacement. If the thinner center of the scar is insufficiently strong to withstand the incessant systolic build-up of the intraventricular pressure, bulging and formation of aneurysm will ensue. Occasionally the necrotic area will become so softened that it will rupture (fatally) before the healing process has begun.

Surgical Considerations

Indirect Methods: In the past, efforts to influence the course of coronary atherosclerosis



4 5

FIG. 4. Original retrograde approach to a localized atheromatous lesion of the coronary artery. A curette-like instrument was inserted by way of an expendable terminal tributary of the anterior descending branch.

FIG. 5. Antegrade approach through the coronary ostia by way of the opened aortic root. Complete cardiopulmonary bypass is required in this technic.

have taken four forms: (1) Palliative, such as the various sympathectomy procedures,[13] partial or total thyroidectomy[14] and perhaps ligation of the internal mammary;[15] (2) application of vascularized contiguous tissues to the abraded surface of the heart;[16] (3) those measures deemed capable of augmenting the size of the intercoronary collateral pathways, such as ligation of one or more of the coronary veins,[17] intrapericardial instillation of chemical irritants[18] and arterialization of the coronary sinus;[19] and (4) implantation of the cut bleeding end of the left internal mammary artery into the thickness of the left ventricular wall (Vineberg[20]). Of these, only the last measure can be considered to be capable of contributing a significant increment of additional blood supply to the ischemic myocardium. In practice, since the internal mammary artery is not large, it may be subject to kinking or thrombosis and, hence, the grafted vessel may fail to function. As yet, in spite of many attempts by various authors,[21,22] none of the plastic prosthetic tubes has proved more satisfactory than the internal mammary artery for the purpose of introducing additional blood directly into the spongy structure of the myocardium.

These more or less indirect and non-definitive methods of intervention for occlusive disease of the coronary arteries would seem to be closely analogous to the various nerve blocks, sympathetic denervations and periarterial neurectomy procedures which once were applied widely in occlusive disease of the arteries of the extremities. Following the pioneering efforts of Dos Santos,[32] Cassel,[33] Guthrie[34] and others, these now have been replaced largely by the more definitive procedures of endarterectomy or thromboendarterectomy, or resection and replacement of the affected arterial segment with a vascular graft or a prosthetic tube. It seems probable to us that a similar transition from the indirect non-definitive types of surgery for coronary disease to direct definitive attacks upon the diseased arterial segment is imminent. The obvious disinclination of cardiologists and internists to refer their patients for any of the non-definitive types of procedure serves to emphasize their dissatisfaction with the relatively limited benefits which are derived from them.

Direct Surgical Methods: Undoubtedly, direct attacks upon the diseased coronary arteries will likewise take the forms of endarterectomy (or thromboendarterectomy) procedures or excision with graft or prosthetic replacement of the excised segment. It is conceivable that bypass procedures in which blood from an extracardiac artery may be introduced by way of a prosthetic

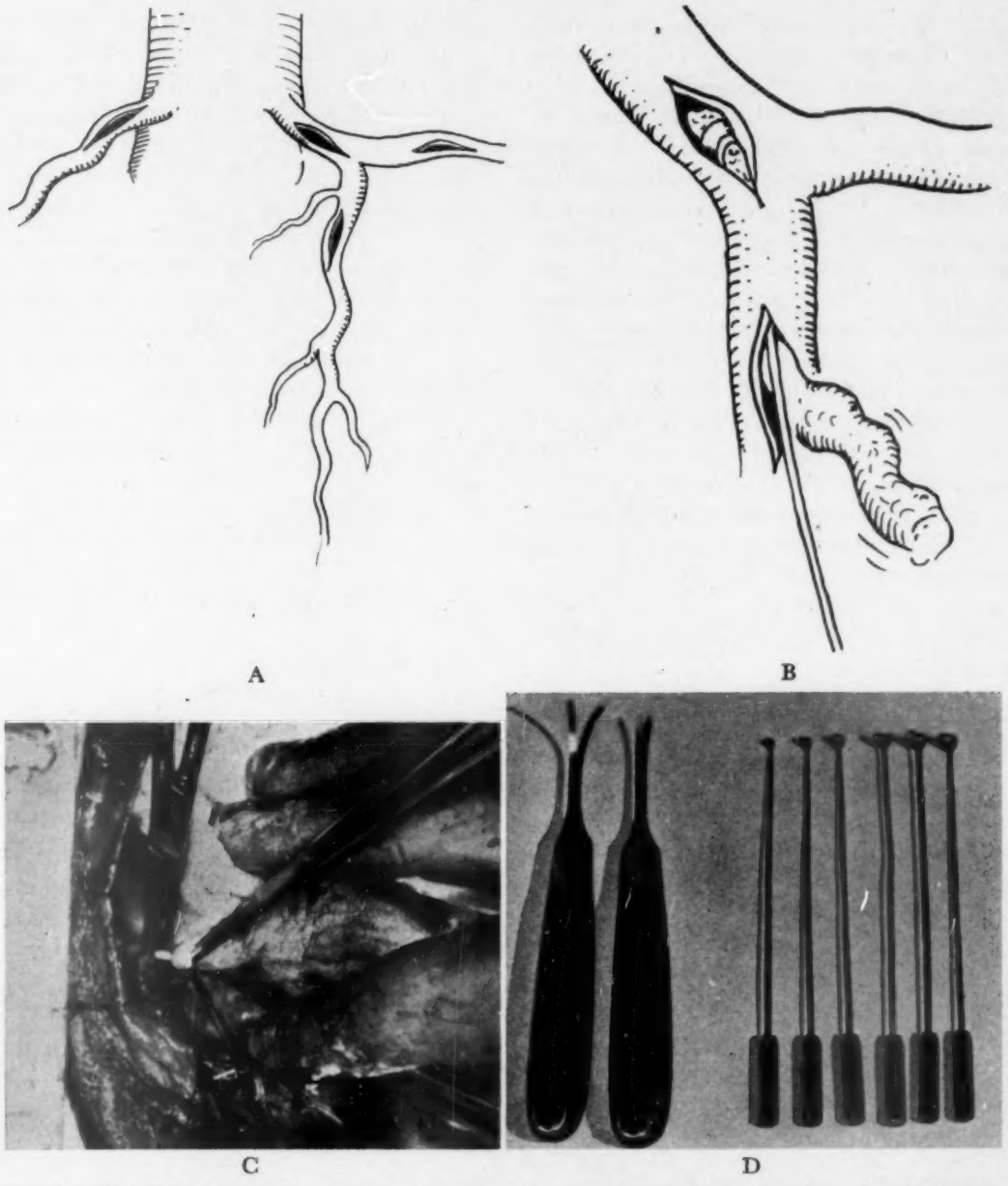


FIG. 6. The direct performance of a coronary endarterectomy requires complete circulatory bypass. A, sites of primary incision of the various major coronary arteries in endarterectomy procedures. B, multiple small incisions of the affected coronary artery are utilized when necessary to remove a long segment of atherosclerotic intima, perhaps with a contained thrombus. C, operative photograph showing surgical elevation of dissected intima and contained thrombotic cast from incised right coronary artery in patient F.C. D, Lemmon coronary dissectors and graduated endarterectomy loops. (Obtainable from G. P. Pilling & Sons, Philadelphia, Pennsylvania.)

tube or vascular graft to the lumen of a coronary artery at a site distal to an occlusion also may have a place.[23,24] While we have investigated each of these approaches in the animal laboratory, to date the only direct operations for coronary artery disease which we have performed clinically have been of the endarterectomy or thromboendarterectomy type. This type of procedure upon the obstructed coronary artery seemed so logical and so readily feasible of accomplishment that we are currently directing maximal attention toward the perfection of specific diagnostic and ancillary measures and further improvement in the surgical technic. Warren's[25] experience with peripheral atherosclerosis also favors this type of approach over resection and replacement of vascular segments.

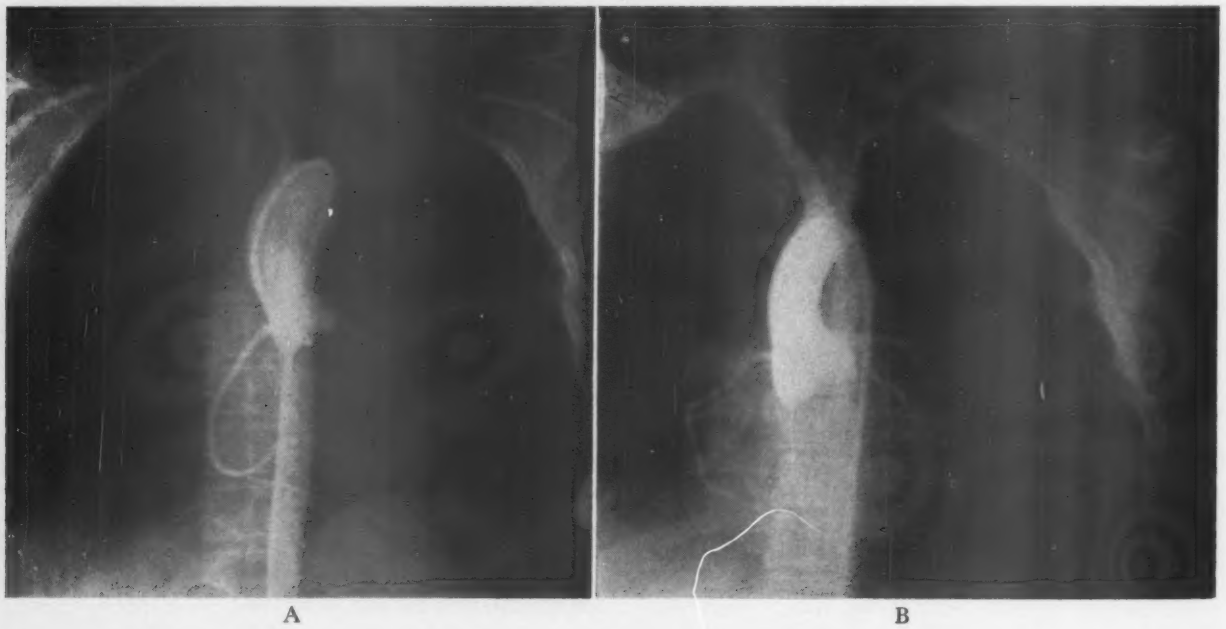
Coronary Endarterectomy: Historically, the first operative survival from an attempt at endarterectomy in October 1956 was reported from

our clinic.[26] It was thought subsequently that the technic (retrograde) employed in that case left much to be desired. Further investigation of the problem both in the animal laboratory and in the autopsy room led logically to successive development of the technic through the following stages: (1) the retrograde approach using an "expendable" branch of the affected coronary artery without circulatory bypass (Fig. 4); (2) direct entrance into the coronary ostia through the opened ascending aorta using the conventional heart-lung bypass (Fig. 5); (3) direct attack at the site (or sites) of obstruction of the affected artery (Fig. 6) using the "autogenous lung" bypass of Blanco et al.[27] and hypothermia. Great effort has been directed to prevention of postoperative thrombosis at the site of vascular traumatization by attempting to remove all lesions from the tributary "run-off" branch vessels as well as from the affected major artery, and by the use of anticoagulants and plasmin.

Longmire and Cannon[28] have recently reported their experience with five direct operations for coronary atherosclerosis.

X-ray Visualization of Coronary Arteries Pre- and Postoperatively: Part of our caution in pursuing the direct operative approach may be attributed to the unhappy fact that the usual clinical and laboratory measures for making a definite diagnosis of coronary artery disease allow a significant margin for error, especially in those seemingly ideal patients who are in the "prodromal" or preocclusive (anginal) stage of coronary insufficiency, not yet having suffered a myocardial infarction and muscle damage. It would be most advantageous if a given specific diagnostic measure were capable both of localizing the site of the lesion and quantitating the degree of obstruction. Then, restudy in the postoperative period would enable the surgeon and clinician alike to evaluate the effectiveness of various possible operative procedures.

Direct visualization of the opacified coronary arterial pattern by radiographic means[29] would seem to satisfy these requirements most nearly. Great progress has been made in this direction both at our clinic and elsewhere[30] during the months since the first clinical coronary endarterectomy procedure was carried out. While still further refinements in these technics undoubtedly are in the offing, at the present moment we have at hand a safe and practical method for study of coronary arterial patency both before and after surgery. The importance of this facility and its routine employment may be appreciated more fully in light of the fact that during the three months prior to submission of this presentation, three patients, one man and two women, have come to us with a superficially convincing



A B

FIG. 7. A, visualization of architecture of normal (right coronary preponderant) coronary arterial trunks in patient E.R., a white woman who had been subjected erroneously, at another hospital, to two previous (non-definitive) operations for "coronary artery disease." B, visualization of normal coronary arterial pattern in patient V.T., a white man who presented a fairly convincing complaint of "angina pectoris."

history of coronary arterial disease. One already had been subjected elsewhere to two different "revascularization" operations for "coronary artery disease" without clinical benefit. Coronary arteriography revealed a normal vascular pattern in each patient (Fig. 7).

On the other hand, in patient A. P., a thirty-seven year old vigorous looking meat cutter, the history of angina pectoris in the absence of electrocardiographic changes even upon exercise (Fig. 8) was so unconvincing to our cardiologists that it was not until his third admission to the hospital that coronary arteriography was performed. Even then we were so dubious as to the cause of the incomplete filling of the right coronary artery that we insisted upon performing the study on two separate occasions (Fig. 9A). At operation a nearly completely obstructing partially organized thrombus was found within the right coronary artery, as well as a recanalized older thrombus extending from the first portion of the left main coronary artery to the most distal ramifications of the anterior descending branch. It seemed remarkable that so much disease could exist in the presence of a normal electrocardiogram. Removal of these thrombi along with the intimal coats of the affected vessels and repair

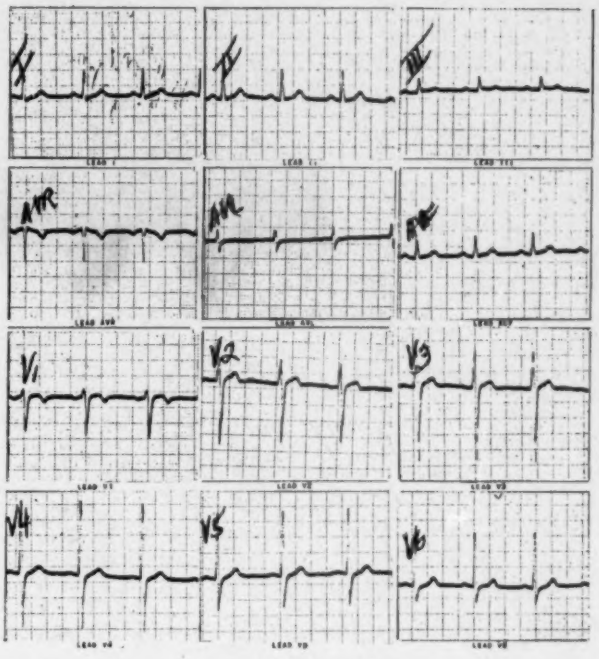
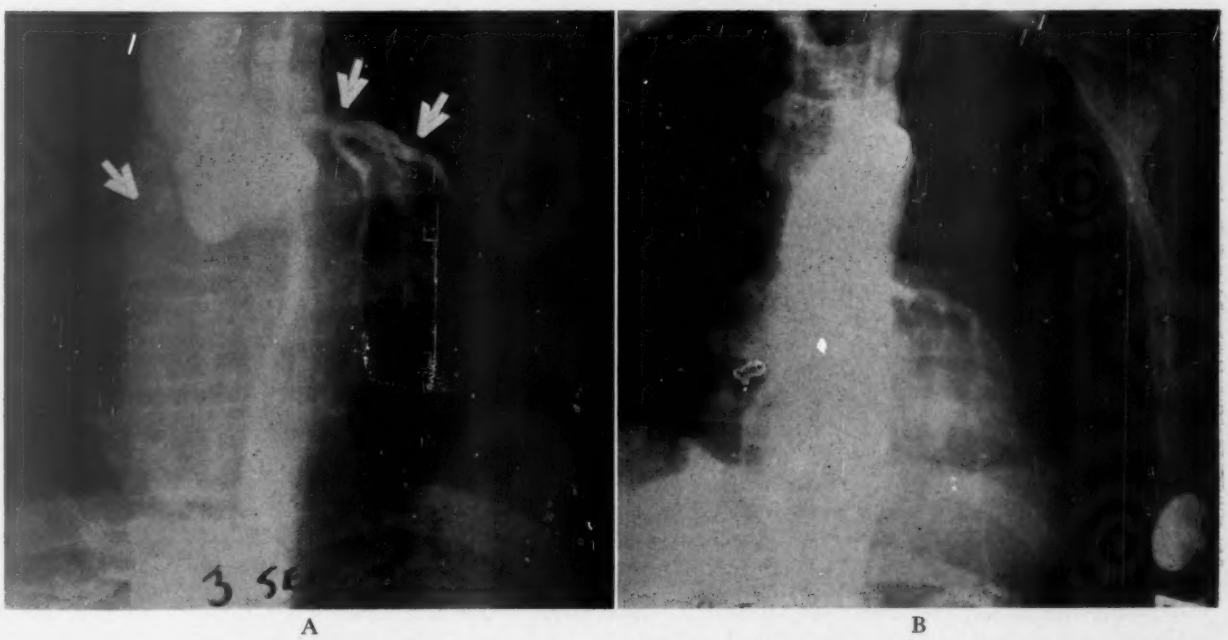


FIG. 8. Normal (preoperative) electrocardiographic pattern obtained from patient A.P., a thirty-seven year old white man who presented a history of pain in the chest which resembled angina pectoris. The tracing did not change after exercise. The extensive pathologic lesions removed from this man (Fig. 10) were evidently compatible with a normal electrocardiogram. The late postoperative electrocardiogram was unchanged.



A B

FIG. 9. A, coronary arteriogram obtained from patient A.P. This study was repeated on a second (preoperative) occasion with identical findings. Note the poor filling of the right coronary artery (arrows). The septal branch of the left coronary artery is not visualized. A large accessory branch of the left anterior descending trunk is filled but the latter trunk is scarcely recognizable. B, postoperative coronary arteriogram from patient A.P. showing good filling of the previously poorly visualized right coronary artery, the anterior descending branch of the left coronary and the septal branch.

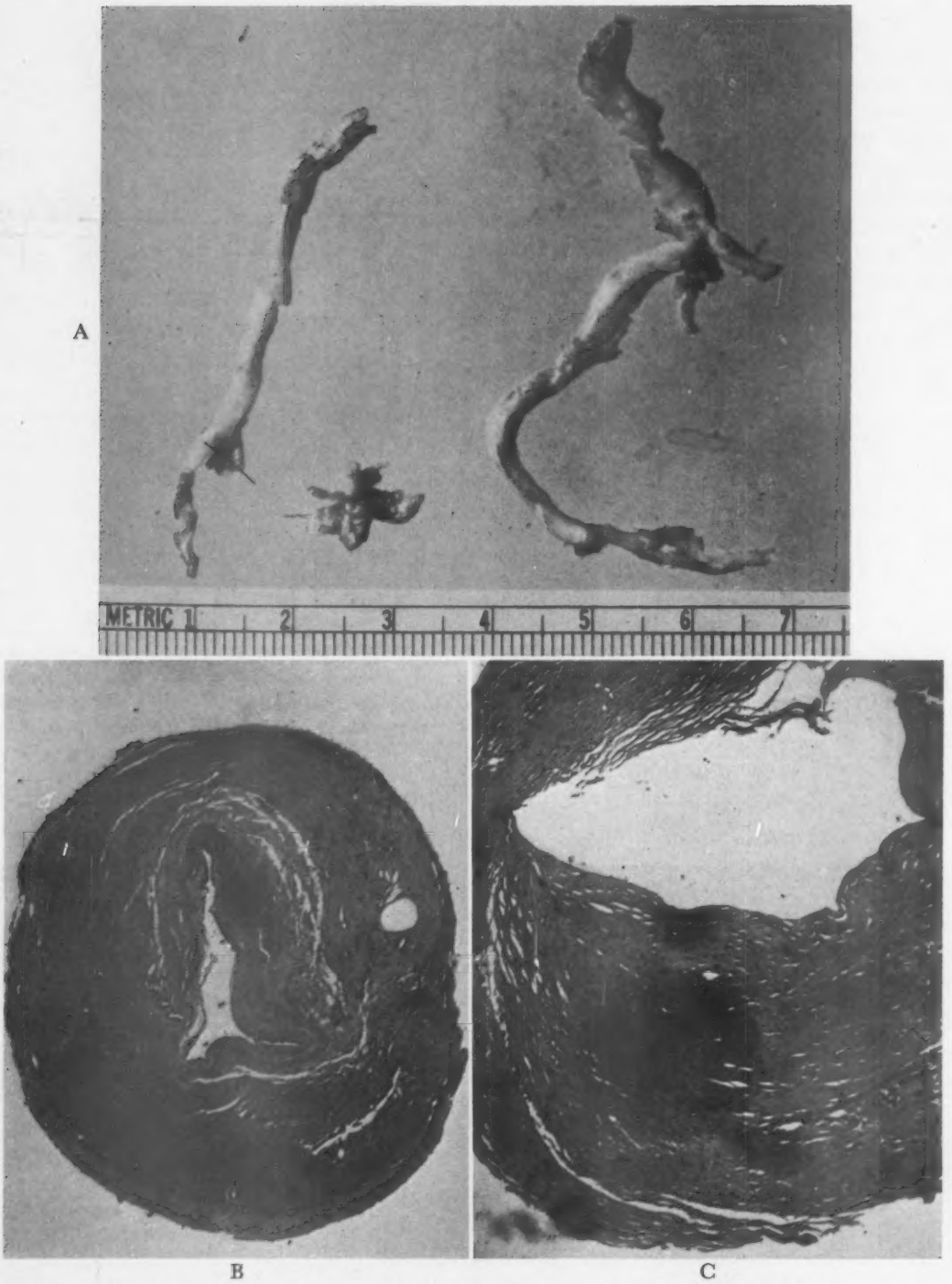


FIG. 10. A, extensive thrombotic casts (with encasing intima) removed from the right coronary artery (on the left) and from the left main coronary and anterior descending branch (on the right) of patient A.P. There were but small projections of the lesion into the left circumflex and septal branches. B, photomicrograph of cross-section of right coronary arterial cast from patient A.P. showing small central recanalized lumen. C, photomicrograph of cross-section of cast from anterior descending coronary artery in patient A.P. Note larger recanalized lumen.

of the remaining wall of the vessel was carried out without untoward incident (Fig. 10). The patient's recovery was uneventful. Postoperative coronary arteriography revealed excellent patency of all major branches (Fig. 9B). The postoperative electrocardiogram (early) revealed the usual changes associated with intrapericardial surgery, but since has reverted to a

fully normal pattern. The patient reports complete relief of anginal pain.

Chances of Recurrence of Lesions: A question always properly raised in any discussion of endarterectomy for atherosclerotic lesions is: Will atheromatous lesions not tend to reform eventually in the wall of the traumatized vessels? If so, of what permanent value is the operation? Obviously we do not know the full answer to such questions. Presently, it would seem that unless we develop a good medical method for the prevention of atherosclerosis that such recurrence is possible. However, the period before recurrence takes place probably will be long, and the patient will be protected significantly during the interim period. If dietary restriction, especially with regard to animal fats and total caloric intake, is truly capable of preventing future deposition of lipids in the arteries, such a major surgical intervention, even though ideally successful, might well serve as a factor of strong moral suasion against further indiscretion or excess on the patient's part.

Indications for Coronary Endarterectomy

In addition to a proper radiographic demonstration of the existence of actual coronary arterial lesions, it is obvious that the patient must meet certain clinical requirements for such a major surgical undertaking. Ideally we should prefer a relatively young and vigorous subject with a well marked anginal syndrome but without significant complication and without a history of myocardial infarction or electrocardiographic evidence of the same. Such a patient may be considered to be in the prodromal or preinfarctional stage like patient A. P. and, hence, capable of restoration to full normal myocardial health (Figs. 9 and 10).

Less ideally one might accept a similarly vigorous subject who has suffered from but one episode of myocardial infarction but who continues to present or perhaps after the elapse of months or years represents himself with recurrence of typical anginal pain on effort. Obviously, nothing can be done to salvage that portion of his myocardium which has undergone necrosis and fibrous replacement. But the anginal pain (if true) represents the complaint of an additional area of ischemic myocardium which has not yet undergone necrosis. In other words, the pain is prodromal with respect to an impending completion of a new site of occlusion of an additional arterial branch. In this type of case it is deemed essential that the heart should not be enlarged significantly and that heart failure should not be present.

Patients with a definite history of two or more bouts of infarction would represent significantly less desirable candidates for surgical intervention. However, it might be considered that they may be even more desperately in need of restoration of full-sized channels in those coronary arterial trunks which remain. Obviously only the passage of much more time and the experience which will accrue therefrom can establish a sound line of delineation between operability and non-operability in advanced coronary atherosclerosis.

Contraindications to Endarterectomy

In general, the older the patient the more likely the disease to be diffuse, and the less suitable the patient for a direct coronary intervention both from the local and the general viewpoints. In similar lesions affecting arteries elsewhere in the body[31] it has been noted that after the elapse of some years an intimal thrombus becomes densely organized and the entire vessel becomes contracted and cord-like so that removal of the intima and its contained thrombus becomes technically impossible. With the passage of time atheromatous lesions often undergo calcific change which may so invade the wall of the vessel that it necessarily would become destroyed during any attempt at removal of the intima. On the other hand, new lesions may develop for the first time in older patients and presumably would lend themselves as well to removal as in the younger patients.

Perhaps as a seemingly reasonable working basis at this admittedly premature point in medical history, we might establish the age of sixty years as the upper limit of permissible operability. Similarly, we might refuse surgery to any patient in frank heart failure or one with cardiac enlargement more than grade 2 plus. Presumably such hearts are extensively fibrosed. A diastolic gallop rhythm likewise might be contraindicative to surgical intervention.

Such complicating factors as hypertension, diabetes, renal disease, conduction defects or a history of a relatively recent episode of infarction (within two months) might well serve as deterrents to surgery even though not actually contraindicative in certain specific patients. A significant elevation of the serum cholesterol should not contraindicate surgical intervention although it might augur ill for the patient's long term fate. Certainly it would tend to indicate

TABLE I
Subjective Results in Thromboendarterectomy

Result	No.
Operative death	2
Same	0
Slightly improved*	3
Moderately improved	4
Markedly improved	6
Total	15

* One patient died eight months after operation because of occlusion of the right coronary (unoperated) artery.

TABLE II
Objective Results of Thromboendarterectomy

Result	No.
Operative death	2
Same	1
Fair*	4
Good	4
Excellent	4
Total	15

* One patient died eight months postoperatively because of occlusion of the right coronary (unoperated) artery after fair improvement from operation.

TABLE III
Coronary Arteries Operated on Directly

Artery	No.
Left main only	0
Left main and anterior descending	3
Anterior descending only	5
Left circumflex and anterior descending	2
Left circumflex, anterior descending, main and right coronary	2
Right coronary only	3
Total	15

the desirability of extreme dietary restrictive measures for an indefinite period postoperatively.

Results of Endarterectomy

As mentioned previously, we have attempted endarterectomy or thromboendarterectomy in fifteen patients to date. However, we are not satisfied with the surgical accomplishment in several of the earlier patients. Thirteen patients survived operation. One patient (L. C.), in whom only the anterior descending coronary artery was treated, died eight months following seemingly successful surgery (from an acute occlusion of the right coronary artery). This unhappy experience has convinced us that all affected branches of both coronary arteries should be relieved of their obstructing lesions at the time of the original intervention.

The series included thirteen men and two women, the former ranging from thirty-seven to fifty-seven years of age and the latter being twenty-eight and thirty-five years, respectively.

Table I presents the subjective improvement reported by the surviving patients. Table II, in contrast, presents the evaluation of the attending cardiologists. Table III shows the coronary arteries operated upon in these fifteen patients.

Summary and Conclusions

The problem of coronary artery disease is reviewed from the surgical standpoint in the light of our present thinking and understanding of the disease. Present considerations in the evaluation and selection of patients for coronary thromboendarterectomy are discussed. Certain technical aspects of operations for chronic coronary arterial obstruction have been mentioned.

Results of the operations performed thus far have been presented and indicate that the operation is technically possible with excellent results in properly selected patients. This is the only operation so far performed for coronary artery disease which directly attacks and attempts to remove the pathologic condition. While long term evaluation of the patients remains to be determined, the operative results to date have been encouraging and further trial of the procedure would seem to be indicated.

Acknowledgments

All roentgenograms are reproduced by courtesy of Dr. J. S. Lehman, Professor and Head of the Department of Radiology, Hahnemann Medical College and Hospital. The photomicrographs and their interpretation are published with permission of Dr. J. E. Imbriglio, Professor of Pathology, Hahnemann Medical College and Hospital, Philadelphia, Pennsylvania.

References

1. Vital Statistics of United States, 1949, Part 1: Place of Occurrence, pp. 102, 109. Washington, D. C., 1951. Federal Security Agency, Public Health Service, National Office of Vital Statistics.
2. Vital Statistics of the United States, 1956, Vol. II, Mortality Data, p. 23. Washington, D. C., 1958. U. S. Dept. of Health, Education and Welfare,

Public Health Service, National Office of Vital Statistics.

3. Welch, J. S., Kirklin, J. W., Ellis, F. H., Jr. and Brewer, A. J. Resection and grafting for chronic occlusion of terminal aorta or iliac arteries. *J.A.M.A.*, 164: 1045, 1957.
4. DeBakey, M. E., Crawford, E. S., Cooley, D. A. and Morris, G. C., Jr. Surgical consideration of occlusive disease of the abdominal aorta and iliac and femoral arteries. Analysis of 803 cases. *Ann. Surg.*, 148: 306, 1958.
5. Cannon, J. A., Barker, W. F., and Kawakami, I. G. Femoral popliteal endarterectomy in treatment of obliterative atherosclerotic disease. *Surgery*, 43: 76, 1958.
6. Lyons, C. and Galbraith, G. Surgical treatment of atherosclerotic occlusion of internal carotid artery. *Ann. Surg.*, 146: 487, 1957.
7. Dock, W. The predilection of atherosclerosis for the coronary arteries. *J.A.M.A.*, 131: 875, 1946.
8. Beck, C. S. Coronary artery disease: physiologic concepts: surgical operation. *Ann. Surg.*, 145: 439, 1957.
9. Schlesinger, M. J. and Zoll, P. M. Incidence and localization of coronary artery occlusions. *Arch. Path.*, 32: 178, 1941.
10. White, N. K., Edwards, J. E. and Dry, T. J. The relationship of the degree of coronary atherosclerosis with age in men. *Circulation*, 1: 645, 1950.
11. Schlesinger, M. J. An injection plus dissection study of coronary artery occlusions and anastomosis. *Am. Heart J.*, 15: 528, 1938.
12. Blumgart, H. L., Schlesinger, M. J. and Zoll, P. M. Angina pectoris, coronary failure and acute myocardial infarction. The role of coronary occlusions and collateral circulation. *J.A.M.A.*, 116: 91, 1941.
13. Jonnesco, T.: Angine de poitrine guerie par la resection du sympathique cervico-thoracique. *Bull. Acad. Med., Paris*, 84: 93, 1920.
14. Blumgart, H. L., Levine, S. A. and Berlin, D. D.: Congestive heart failure and angina pectoris. The therapeutic effect of thyroidectomy on patients without clinical or pathological evidence of thyroid toxicity. *Arch. Int. Med.*, 51: 866, 1933.
15. Glover, R. P., Davila, J. C., Kyle, R. H., Beard, J. C., Trout, R. A. and Mitchell, J. R. Ligation of the internal mammary artery as a means of increasing blood supply to the myocardium. *J. Thoracic Surg.*, 34: 661, 1957.
16. Carter, B. N. Discussion of Beck, C. S. Revascularization of the heart. *Ann. Surg.*, 128: 861, 1948.
17. Gross, L., Blum, L. and Silverman, C. Experimental attempts to increase the blood supply of the dog's heart by means of coronary sinus occlusion. *J. Exper. Med.*, 65: 91, 1937.
18. Thompson, S. A. and Raisbeck, M. J. Cardiopericardiopexy. *Ann. Int. Med.*, 16: 495, 1942.
19. Beck, C. S., Stanton, E., Batiuchek, W. and Leiter, E. Revascularization of the heart by graft of a systemic artery or a new branch from the aorta into the coronary sinus. *J.A.M.A.*, 137: 436, 1948.
20. Vineberg, A. M. Development of anastomosis between coronary vessels and transplanted internal mammary artery. *Canad. M. A. J.*, 55: 117, 1946.
21. Massino, C. and Boffi, L. Myocardial revascularization by a new method of carrying blood directly from the left ventricular cavity into the coronary circulation. *J. Thoracic Surg.*, 34: 257, 1957.
22. Sabiston, D. C., Jr., Fauteux, J. P. and Blalock, A. An experimental study of the fate of arterial implants in the left ventricular myocardium with a comparison of similar implants in other organs. *Ann. Surg.*, 145: 927, 1957.
23. Absolom, L. B., Aust, J. B., Varco, R. L. and Lillehei, C. W. Surgical treatment of occlusive coronary artery disease by endarterectomy or anastomatic replacement. *Surg., Gynec. & Obst.*, 103: 180, 1956.
24. Julian, O. C., Dye, W. S., Olwin, J. H. and Jordan, P. H. Direct surgery of arteriosclerosis. *Ann. Surg.*, 136: 459, 1952.
25. Warren, R. and Villaercencio, J. L. Ileofemoropopliteal arterial reconstructions for arteriosclerosis obliterans. Factors influencing late patency. *New England J. Med.*, 260: 255, 1959.
26. Bailey, C. P., May, A. and Lemmon, W. M. Survival after coronary endarterectomy in man. *J.A.M.A.*, 164: 641, 1957.
27. Blanco, G., Oca, C., Lagana, S., Nunez, L. E., Schaefer, J. and Bailey, C. P. Autogenous lung oxygenation during cardiac bypass. *Am. J. Cardiol.*, 2: 302, 1958.
28. Longmire, N. P., Cannon, J. A. and Kattus, A. A. Direct vision coronary endarterectomy for angina pectoris. *New England J. Med.*, 259: 993, 1956.
29. Lemmon, W. M., Lehman, J. S., Bailey, C. P. and Kimel, J. Use of an artificial pacemaker in acetylcholine-induced cardiac arrest for coronary arteriography. Proceedings of the 29th Scientific Session, American Heart Association, p. 726, 1959.
30. Dotter, C. T. and Frische, L. H. Visualization of the coronary circulation by occlusion aortography. A practical method. *Radiology*, 71: 502, 1958.
31. Crawford, E. S. Personal communication.
32. Dos Santos, J. C. Sur la disobstruction des thromboses arterielles anciennes. *Mém. Acad. chir.*, 73: 409, 1947.
33. Cassel, A. Results of transplantation of blood vessels, organs, and limbs. *J.A.M.A.*, 51: 1662, 1908.
34. Guthrie, C. C. Blood Vessel Surgery and Its Applications, p. 91. London, 1912. E. Arnold.

Rupture of the Heart in Myocardial Infarction

Clinical and Pathologic Observations*

LOUIS H. SIGLER, M.D., F.A.C.C.

Brooklyn, New York

RUPTURE of the heart in myocardial infarction is not frequent. Edmondson and Hoxie[1] found only seventy-two cases in 25,000 autopsies performed in seventeen years at the Los Angeles County Hospital. All occurred in myocardial infarction, giving an incidence of 8.3 per cent of rupture in infarction. In the Massachusetts General Hospital, Friedman and White[2] found only ten cases of cardiac rupture (9.3 per cent) in acute infarction. In 1,026 autopsies of persons who had myocardial infarction reviewed by Oblath and co-workers,[3] there were seventy-two instances of cardiac rupture (7.11 per cent). Wessler and co-workers[4] in a review of the literature found cardiac rupture in 9 per cent of 2,609 cases of myocardial infarction observed in twenty-nine general hospitals. In 114 autopsies of patients who had acute myocardial infarction reported by McDonnieal and co-workers,[5] twelve cases of rupture or 10.5 per cent were observed.

Many instances of cardiac rupture in myocardial infarction have been observed in people who died suddenly without any history of acute infarction. Martland[6] reported forty-two instances (13.8 per cent) of rupture of the heart in 304 cases of coronary occlusion among 2,000 autopsies which he performed. The incidence is far greater in mental institutions where no clear-cut symptoms of coronary occlusion are obtainable from the patients. Jetter and White[7] found rupture of the heart in sixteen (73 per cent) of twenty-two cases of infarction. Emotional strain associated with mental disturbances beside the lack of clear-cut symptomatology may be a factor.

Within the past two years we have observed eight cases of cardiac rupture in acute myocardial infarction at the Adelphi Hospital, the findings of which are briefly summarized.

CASE REPORTS

CASE 1. L. N. a seventy-three year old woman, was admitted with a history of hypertension. Nine hours before admission she experienced sharp pains in the anterior part of the chest radiating to the back and she vomited twice. On admission she presented marked pallor. The heart rate was 88 beats per minute and regular. The blood pressure was 95/60 mm. Hg. The abdomen was somewhat distended. Soon after admission she became cyanotic and dyspneic and died.

Autopsy showed marked hemopericardium. The heart weighed 500 gm. Moderate atherosclerosis was found in all coronary arteries. About 2 cm. from the ostium of the anterior descending branch of the left coronary artery, there was a fresh thrombus at an atheromatous plaque and another fresh thrombus 2 or 3 mm. beyond that. At the latter area the entire thickness of the left ventricle showed a ragged tear. No gross myocardial infarction was present.

CASE 2. J. K., a fifty-three year old man, experienced pressing pain in the anterior part of the chest one week before admission. The pain appeared after a heavy meal and on walking as little as one block. One day before admission the pain appeared spontaneously in a more severe form and radiated to the interscapular region and to both shoulders and arms, and was accompanied by cold sweat and pallor. The blood pressure was 180/100 mm. Hg. An electrocardiogram revealed depression of the S-T segment in leads I, aVL and V_4. The pain continued throughout the night and he was admitted to the hospital at 9 A.M. On admission the heart rate was 100 beats per minute and regular, with an occasional premature contraction. The heart sounds were of fair quality. Examination of lungs and abdomen revealed no abnormalities. He died suddenly four and one-half hours after admission.

* From the Cardiac Service, Adelphi Hospital, Brooklyn, New York.

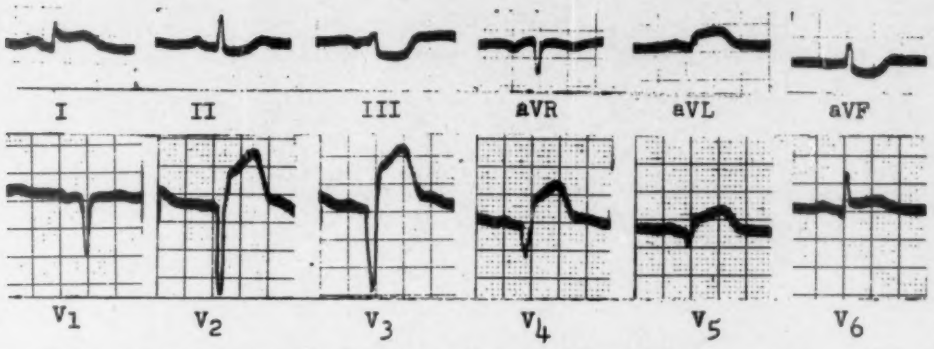


FIG. 1. Case 2. Early phase of acute infarction of anterior left ventricular wall.

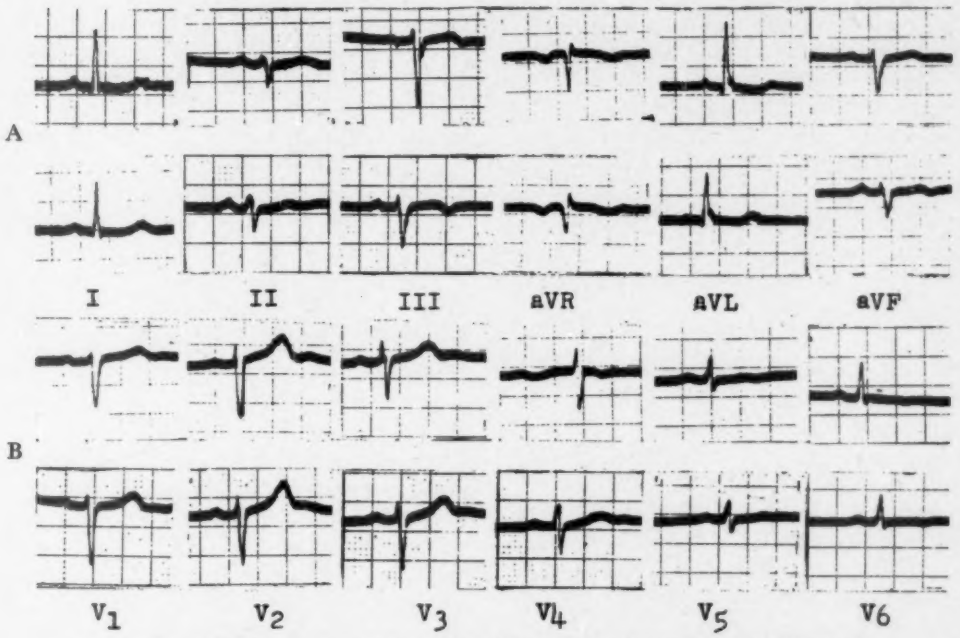


FIG. 2. Case 3. Myocardial ischemia, anterolateral wall of left ventricle.

An electrocardiogram (Fig. 1) obtained about two hours before death revealed an early phase of acute anterior myocardial infarction.

Autopsy showed considerable hemopericardium. The heart weighed 420 gm. A hemorrhagic area measuring 1.6 by 0.6 cm. was found on the anterior surface of the left ventricle. Lacerations and recent hemorrhages were seen, extending through the entire thickness of the muscle of the left ventricle from the apex close to the interventricular septum to the lacerated and hemorrhagic area on the anterior wall. The coronary arteries showed scattered atheromatous plaques. At an area beginning about 3 cm. from the ostium of the anterior descending branch of the left coronary artery, a fresh thrombus completely occluded the vessel.

CASE 3. L. L., a sixty-three year old woman, was admitted with a history of hypertension of long standing. Eight months previous to admission she began to experience pain in the anterior part of the chest on walking outdoors which was relieved by rest. The pain became more severe about three weeks before admission. On the day of admission she developed spontaneous severe "squeezing" pain in the anterior part of the chest radiating to the neck and both shoulders. This pain recurred on and off while in the hospital. Nitroglycerin and pentaerythritol tetranitrate gave some relief. Her heart was not enlarged; the rate was 100 per minute and regular and the sounds were of fair quality. The blood pressure varied between 100/60 and 120/78 mm. Hg. The blood transaminase on the following day was 33 units, on the third day, 25 units and on the fourth day, 23 units. The blood count was normal. Her temperature ranged between 99 and 100°F. She had received anticoagulant therapy but at no time was her prothrombin time higher than twenty-four seconds with a control of thirteen seconds.

Electrocardiograms were obtained on the day of admission (Fig. 2A) and the following day (Fig. 2B). Both tracings showed only some degree of myocardial ischemia of the anterolateral wall of the left ventricle, and a horizontal electrical position of the heart.

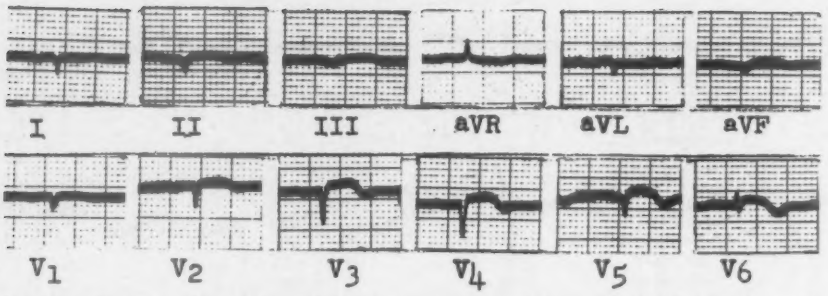


FIG. 3. Case 4. Infarction of the anteroseptal and lateral left ventricular wall and possible damping effect of pericardial effusion.

Four days after admission she was given an enema and while still on the bedpan she complained of severe pain in the chest and became very dyspneic. She went into complete shock, did not respond to any medication and died within ten minutes.

Autopsy revealed marked hemopericardium. A laceration of the anterolateral portion of the left ventricle 1 cm. long and 0.5 cm. wide was found which communicated with the cavity of the left ventricle. The heart weighed 310 gm. The heart muscle surrounding the lacerated area was soft and congested. The coronary arteries were patent throughout with some narrowing in certain areas by atheromatosis.

CASE 4. A. L., a sixty-nine year old woman, who never had any symptoms referable to her heart, experienced severe recurring pain in the precordial region radiating to the left interscapular area with some dyspnea six days before admission. The pain became more acute and severe on the day of admission. Her heart rate was 88 per minute, the rhythm was regular, heart sounds were very distant and blood pressure was 140/90 mm. Hg. The leukocyte count was 13,600, hematocrit was 38 per cent and hemoglobin was normal. The blood pressure diminished gradually to 108/70 mm. Hg.

An electrocardiogram on the day of admission (Fig. 3) revealed evidence of anteroseptal and lateral infarction of the left ventricle and low voltage complexes which suggested a possible damping effect of pericardial effusion.

While on the bedpan the day after admission, she suddenly collapsed and died immediately.

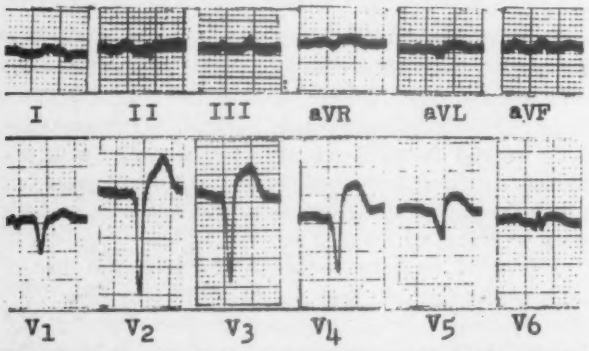


FIG. 4. Case 5. Infarction of the anterior left ventricular wall.

At *autopsy*, the heart weighed 390 gm. and the pericardial cavity contained about 250 cc. of free blood. There was an area of infarction and laceration in the anterior wall of the left ventricle near the apex, with dark red clotted blood and fibrinous material covering that area. The anterior wall of the right ventricle immediately near the apex and including the interventricular septum in that region showed a laceration about 0.7 cm. long. The coronary arteries showed scattered atheromatous plaques and a recent thrombus in the anterior descending branch of the left coronary artery was found, beginning about 2.5 cm. from the ostium, completely occluding the lumen. The aorta showed scattered calcified plaques.

CASE 5. W. W., a seventy-one year old man, was awakened in the middle of the night four days before admission by severe constricting pain in the anterior part of the chest radiating to the left arm which was accompanied by shortness of breath, cold sweat and weakness. The episode lasted about two hours and subsided. He felt well the following two days and then the pain recurred in a more severe form lasting eight hours, not fully relieved by Demerol.® On admission two days later his heart was found to be enlarged. The heart rate was 82 and regular, the heart sounds were of poor quality and the blood pressure was 90/40 mm. Hg. He was not in shock. The physical findings remained the same for the following three days. The leukocyte count was 17,900 with 84 per cent polymorphonuclear cells on the day of admission. On the following day the sedimentation rate was 40 mm. in one hour (Wintrobe). The transaminase was 36 units. The temperature ranged between 99° and 101°F. and the blood pressure remained the same as on admission.

An electrocardiogram (Fig. 4), obtained the day following admission showed acute infarction of the anterior wall. Three days after admission, without the knowledge of the attendants, he left the bed and walked to the bathroom. On the way back he suddenly lost consciousness. His blood pressure recorded by the nurse was 70/52 mm. Hg and his pulse was 110 and irregular. He died a few moments later.

Autopsy showed massive hemopericardium. The heart weighed 500 gm. The myocardium showed

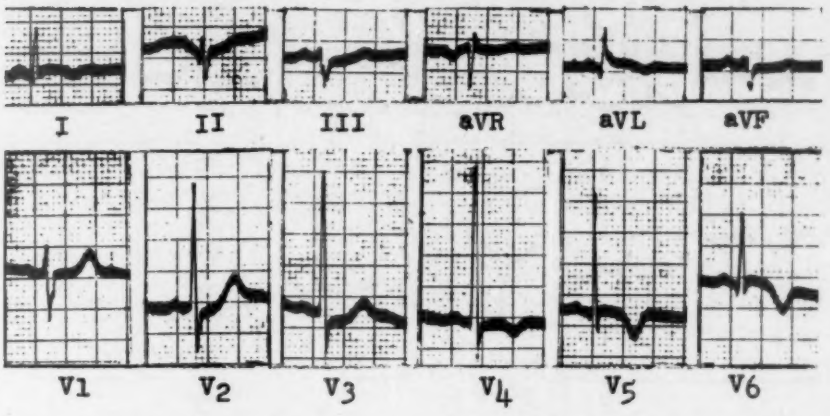


FIG. 5. Case 6. Myocardial ischemia and possible infarction of the anterolateral wall of left ventricle.

grayish-brown softened areas superimposed on dark-red hemorrhagic linear strands. There was a perforated area on the lateral side of the left ventricle 0.5 cm. in diameter covered by thin fibrinous material. A probe could be passed through that perforation into the left ventricle. There was moderate coronary atheromatosis. The anterior descending branch of the left coronary artery, 2 cm. from the ostium, contained brownish-yellow grumous material occluding the lumen.

CASE 6. R. E., a forty-seven year old man, experienced, one week before admission, mild precordial pain radiating to the left shoulder and arm which lasted one hour, then subsided and did not recur. He continued working as a typewriter mechanic without discomfort. The night before admission he returned home from work and after walking up five flights of stairs he experienced shortness of breath and severe precordial pain radiating to the left shoulder and arm accompanied by nausea and vomiting. His symptoms were relieved by nitroglycerin. One hour later a second severe attack of pain with dizziness and weakness developed which recurred on and off during that night and he was admitted to the hospital the following morning. On admission he appeared normal, but complained of recurring pain. His skin was moist and warm. The heart rate was 78 and regular, the sounds were normal and no murmurs were heard. The lungs were clear and examination of the abdomen and extremities showed no abnormalities. The blood pressure was 130/80 mm. A teleoroentgenogram taken the following day showed slight cardiac enlargement and minimal basal congestion. An electrocardiogram (Fig. 5) showed myocardial ischemia and possible infarction in the anterolateral wall of the left ventricle. The leukocyte count was 13,350 with a normal differential; the hemoglobin was normal. The hematocrit was 48 per cent. The sedimentation rate (Wintrobe) was 22 mm. in one hour, and the transaminase was 147 units.

The patient felt fairly well the following four days. His temperature was 100° to 100.6°F. the first two days, and below 100° thereafter. He was receiving anticoagulants but his highest prothrombin time did not exceed twenty-three seconds with a control of thirteen seconds. Five days after admission he suddenly became dyspneic and cyanotic and died before any emergency measures could be applied.

Autopsy showed massive hemopericardium. The heart weighed 390 gm. There was a small ruptured area on the lateral wall of the left ventricle about 1.5 cm. long with roughened margins covered by fibrous material. It communicated with the left ventricular cavity. Section of the heart muscle showed yellowish-gray geographic areas in the region of the anterolateral wall of the left ventricle. The left coronary artery, 3 cm. from its ostium, was completely occluded by grumous material and there was moderate general atheromatosis of both coronary arteries and the main branches.

CASE 7. L. W., a fifty-six year old woman, was admitted with a history of marked hypertension of fifteen years' duration and of diabetes for four years. Six months before admission she had an episode of left heart failure for which she was hospitalized, with good recovery. On the morning of the present admission to the hospital she experienced sudden severe pain in the upper anterior part of the chest radiating to the left arm, accompanied by cold sweat. Her face and lips had a grayish, cyanotic appearance. The heart rate was 82 and respirations 20 per minute; blood pressure was 150/95 mm. Hg. The urine showed 4 plus albumin, 4 plus sugar and 3 plus acetone. The leukocyte count was 16,000 with 90 per cent polymorphonuclear cells; hemoglobin was 80 per cent and hematocrit 47. The blood sugar was 325 mg. per cent.

An electrocardiogram (Fig. 6) showed early anterolateral myocardial infarction.

Eleven hours after admission difficult breathing suddenly developed, and the patient went into complete shock and died a few minutes later.

Autopsy showed hemopericardium consisting of 200 gm. of dark clotted blood and 150 cc. of fluid blood.

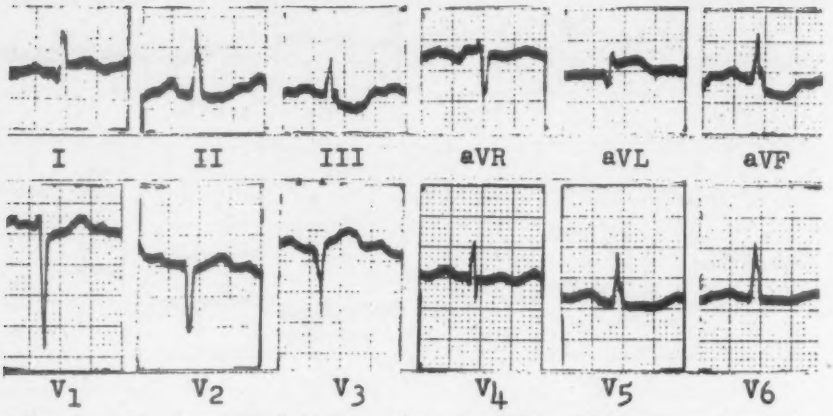


FIG. 6. Case 7. Early infarction of the anterolateral left ventricular wall.

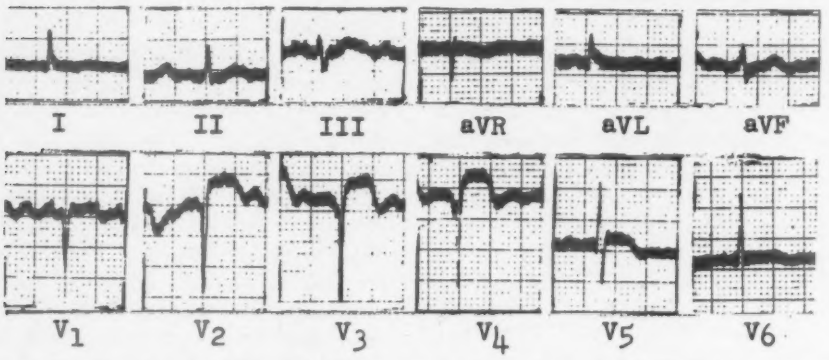


FIG. 7. Case 8. Auricular fibrillation and early acute infarction of the anterior left ventricular wall.

The heart weighed 470 gm. and showed scattered hemorrhagic areas near the apex on the lateral wall. These communicated with lacerated areas through the myocardium extending to the endocardium at the apex and lateral wall. The muscle tissue was soft in these regions. The coronary arteries showed atheromatosis with areas of marked narrowing of the lumen but no complete occlusion was found.

CASE 8. M. S., a seventy-six year old woman, was admitted with a history of low grade hypertension and occasional slight retrosternal pain with weakness of one year's duration. On the day of admission, while doing housework, she was suddenly seized with severe pain in the region of the upper third of the sternum and the corresponding level in the back of the chest, associated with some dyspnea and perspiration. Her blood pressure was 140–150/85–100 mm. Hg. She was rather obese. The heart sounds were of poor quality.

An electrocardiogram (Fig. 7) showed auricular fibrillation and very early acute infarction of the anterior wall. The leukocyte count was 15,700 with 86 per cent polymorphonuclear cells; hemoglobin was 90 per cent and the hematocrit 44 per cent. The sedimentation rate was 32 mm. in one hour (Wintrobe). The blood sugar was 175 mg. per cent. She received 300 mg. of dicumarol and 400 mg. of depoheparin on the day of admission and 100 mg. of dicumarol on the following day when her prothrombin time was eighteen seconds with a control of seventeen seconds. The bleeding time was nine minutes. In the afternoon of the second day of hospitalization she went into shock and died ten minutes later.

Autopsy revealed 200 gm. of clotted blood in the pericardial cavity. The heart weighed 400 gm. There were lacerations of the endocardium of the left ventricle near the apex with linear hemorrhages in the ventricular musculature in that region extending to the lateral pericardial surface of the left ventricle close to the apex. There was moderate coronary atheromatosis and a large atheromatous plaque in the anterior descending branch of the left coronary artery 2.5 cm. from its origin, almost completely occluding the lumen. There was also scattered atheromatosis of the aorta.

COMMENTS

The unusual number of cases of rupture of the heart in myocardial infarction in relation to general autopsies we have had in a short period of time may be partly due to the fact that Adelphi Hospital admits only acute cases. It may, however, be mainly fortuitous. I believe, nevertheless, that if more frequent autopsies were obtained on patients who die suddenly in the early phases of acute myo-

cardial infarction, the incidence of cardiac rupture would be found to be much greater than that reported in the literature to date. I also believe that the incidence of cardiac rupture has progressively increased in the past few years with increase in the incidence of acute myocardial infarction.

LOCATION OF RUPTURE

Rupture of the heart in acute myocardial infarction occurs most frequently in the free wall of the heart at the site of maximum myocardial damage. It most commonly affects the left ventricle and the anterior wall is affected twice as frequently as the posterior wall.[8] It may also involve the adjacent interventricular septum. In occasional cases rupture occurs in the interventricular septum alone, as reported by other authors.[9,10] In extremely rare instances, rupture may be confined to the papillary muscle. Craddock and Mahe[11] observed two such cases in 6,000 autopsies performed in the Baltimore City Hospital and none in 14,000 autopsies performed in Johns Hopkins Hospital. They collected forty-three cases of ruptured papillary muscles and sixty-six cases of perforated interventricular septum from the literature. In the forty-three cases of ruptured papillary muscle, myocardial infarction was the cause in thirty-four cases, periarteritis nodosa in two, trauma in two, ulcerative endocarditis in two, syphilis in one and in two the etiology was unknown.

UNDERLYING CAUSES

Hypertension: There are certain factors observed with sufficient frequency in our patients and in those reported in the literature to consider them underlying causes of rupture of the heart. One is pre-existing hypertension. Of our patients, five gave a definite history of hypertension of long standing. In the remaining three patients, although no such history was obtainable, one patient had a blood pressure of 140/90 mm. Hg on admission and the two others showed some cardiac hypertrophy at autopsy which would speak for possible pre-existing hypertension. Edmondson and Hoxie[1] found a blood pressure of 140/90 mm. Hg or higher in 63 per cent and 160/100 mm. Hg or higher in 32 per cent of patients during the acute phase of infarction where rupture occurred. It is generally felt that rupture occurs three times as frequently if the blood pressure is higher than normal after the onset of infarction.

Sex: Another factor frequently observed is the greater prevalence of rupture in myocardial infarction in women. Although the usual frequency of myocardial infarction in men is about four and one-half times that of women, rupture of the heart in infarction is as frequent or more frequent in women than in men. Of our eight patients, four were women and four were men. In the twelve patients reported by McDonnieal and co-workers[5] eight were women and four were men. The high incidence in women is most likely due to the greater frequency of hypertension in women.

Age: A third factor is that rupture of the heart in infarction never occurs in the younger age groups. In Edmondson's series, rupture did not occur in any person under thirty-nine years of age. Of our patients, one was forty-seven years old; all the rest were above fifty years, the oldest being seventy-six years and the average age sixty-three and a half years. In the series of cases reported by Oblath and co-workers[3] all were over fifty years of age, and in that reported by McDonnieal and co-workers[5] the ages varied between fifty-four and eighty-five years, none being below fifty years.

Duration of Infarction: A fourth and very important factor is the age of the infarct. All reported cases of rupture of the heart in infarction occurred in areas of fresh infarction. To my knowledge, rupture has never been observed to occur in areas of organized infarction, exceptions being the development of a ventricular aneurysm which may occasionally rupture later as in a patient I previously reported[12] where rupture occurred about ten years following infarction. Of 165 patients with old infarction reported by Friedman and White[2] none showed rupture of the heart at autopsy. Of our eight patients, five developed the rupture within ten to thirty-eight hours after the acute onset of infarction, two patients four days and one patient seven days after the onset. In Edmondson's series the average time between the onset of infarction and rupture was 7.4 days. In 78 per cent of patients it occurred between the third and twelfth day and in only 2 per cent of patients did rupture occur after the sixteenth day. These figures are about the same as those found by others.

Physical and Emotional Strain: A fifth and very important factor in the causation of rupture appears to be exposure to some physical and emotional strain in the early phase of myocardial infarction. In our series, rupture of the heart developed in two patients while on the bedpan

and in one after walking to the bathroom and back without the knowledge of attendants. Malamud and Zheutlin[13] reported a case of a fifty-five year old woman in whom rupture of the heart occurred at the site of an infarct four to six days old, following electric shock. Other forms of strain and emotion may be predisposing factors. Frequency of rupture of the heart in infarction among mental patients[7] may serve as an example. Inasmuch as most of the reported cases are based mainly upon the review of the autopsy material without specific clinical observations of possible events that might have taken place before death from cardiac rupture, the question of physical and emotional strain as a cause requires further exploration.

Location of Infarction: A sixth factor might be the location of the acute infarction. It appears that rupture begins close to the apical region of the left ventricle where the musculature is thinnest.

Anticoagulants: A seventh predisposing factor might be anticoagulant therapy. This has been stressed by Aarseth and Lange.[14,15] They found rupture of the heart to be twice as frequent in patients who received anticoagulant therapy than in those who did not. They also observed five instances of hemopericardium without rupture in thirty-three patients who received anticoagulant therapy. Of our patients only three received anticoagulant therapy, in two of whom it might have played a part.

Digitalis: Last, the question of therapy with digitalis as a possible factor has recently been discussed. This may be considered a negligible cause. In none of our patients and in only an occasional case of cardiac rupture reported in the literature has digitalis been used. It is conceivable, however, that the careless use of this drug where not called for and with no proper control may be one of the causes in an occasional case.

MECHANISM OF RUPTURE

The mechanism of rupture of the heart in myocardial infarction is not yet fully understood. On careful review of the pathologic and clinical findings reported by other observers and in our own patients, I am inclined to feel that several factors participate.

Aging of the Myocardium: One factor is the aging process of the myocardium which predisposes to more easy breakdown of the myocardial fibers in advancing age. Cohn[16] demonstrated that in youth the cross striations of the myocardial cells are conspicuous, running like bars to the very edge of the nucleus. In middle life, curious structural elements, known as cement lines, intercalated discs and steplike concentrations appear and the nucleus becomes cloudy. Later, spaces filled with hypochrome pigment appear in the nuclear poles. Such alterations speak for deterioration of the heart muscle fibers with advancing age even in normal conditions.

Hypertension: Another factor is hypertension which produces greater thickness of the individual muscle fibers in the course of time with no corresponding increase in the capillary blood supply, predisposing to a more easy breakdown of these fibers under strain. Coexisting hypertension at the time of infarction may also act directly by increasing the intraventricular pressure.

Local Pathologic Changes: A third and very important factor is the local pathology developing in acute coronary disease. Freeman,[17] in a histopathologic study of thirty-six cases of cardiac rupture in infarction, found multiple subendocardial infarcts surrounded by a very recent transmural infarct associated with a single occlusive thrombosis of a major coronary artery in patients who died within three to seven days after onset. He believes that the older, smaller infarcts are caused by partial obstruction of the major vessel at the site of the final thrombosis. He thinks that the sequence of events leading to rupture consists of focal necrosis following ischemia, then thrombosis of the artery at the site of partial obstruction causing a larger area of infarction and loss of muscular contractility at the site. It may also occur in a transmural infarct more than a few days old where the process of repair is poor. Lunseth and Ruwaldt[18] considered dissecting hematoma to be an important factor in the pathogenesis of rupture in many cases as in dissecting aneurysm of the aorta. They state that the source of the infiltrating hematoma is unknown.

Thrombotic occlusion of one or two coronary vessels occurred in five of our patients; marked narrowing of one area of the anterior descending branch of the left coronary artery by atheromatosis but no thrombosis in two, and in one patient (Case 3), there was moderate atheromatosis with some narrowing, but patent coronary arteries. Ischemic myocardial necrosis and infarction in these patients evidently was caused by prolonged angiospasm, particularly of portions of the vessels which had the greatest degree of atheromatosis.

An important factor in the histopathologic changes in acute coronary disease with myocardial necrosis is probably played also by polynuclear leukocytic infiltration in necrotic areas of the heart. Mallory and White[19] believe that the enzymatic action of these leukocytes reduces the resistance of tissues in those areas and predisposes to rupture.

Impaired Myocardial Contraction: I believe that although each of the above factors plays a great role in the mechanism of cardiac rupture, the greatest part is played by the hemodynamic changes in the process of cardiac contraction and relaxation. In the presence of infarction the involved area does not participate in the contraction during systole. It has been repeatedly shown in the past that while the normal portion of the myocardium undergoes contraction, the infarcted portion expands during systole in an aneurysmal manner. In a recent kinetocardiographic study of forty-two patients with myocardial infarction, Suh and Eddleman[20] demonstrated that aneurysmal bulges or paradoxic outward motions were present at the infarcted area in all patients. These bulges continued throughout the patients' stay in the hospital in 78 per cent of patients; in only 22 per cent did they disappear during the period of hospitalization. Four patients who died and came to autopsy showed no aneurysms. This would indicate that the paradoxic outward motion is a physiologic expansion of the diseased portion of the heart caused by intraventricular pressure during systole.

The impaired contractility of the infarcted area and its stretching during systole evidently produces a suctioning effect in that region helped by the contractile force of the rest of the myocardium which forces the blood outwards in the infarcted area. This process conceivably produces increased pressure in the arterioluminal and arteriosinusoidal vessels, causing rupture of these vessels and a dissecting hematoma which works its way through the entire thickness of the myocardium. It also produces tearing of the diseased myocardial tissue. The condition may be aggravated by a factor such as strain or coexisting hypertension which suddenly throws a greater burden on the heart, increasing the intraventricular pressure.

DIAGNOSIS

Because rupture of the heart is rapidly fatal the recognition of its possible occurrence should be attempted before it happens. Unfortunately, sufficient signs by which we may recognize the condition before it occurs are usually not present. The electrocardiogram is not of value in predicting the occurrence of rupture. In fact, in some cases it may even be misleading in diagnosis of myocardial infarction as in Cases 3 and 6 (Figs. 2 and 5). In an occasional patient (Case 4, Fig. 3), the electrocardiogram suggested possible damping effect of pericardial fluid which could have been construed as being due to slow leakage caused by rupture of the heart.

The actual occurrence of rupture should be suspected in acute myocardial infarction if the patient has hypertension, is over fifty years of age and especially if the patient is a woman, who may suddenly go into complete shock and not respond to therapy, more particularly so if the infarction is in the anterolateral wall. Nuzum[21] observed an eighty-four year old woman with rupture of the heart who presented cycles of normal heart sounds alternating with loud harsh systolic murmurs filling the entire systole. Bishop and Logue[22] observed a loud systolic murmur and thrill in the fourth and fifth left interspaces close to the sternum just before death which was proved at autopsy to be due to laceration of the anterior wall close to the septum. There may be some cases where rupture by dissection occurs relatively slowly with a gradual accumulation of blood in the pericardium giving signs of cardiac tamponade. In such cases, if the parietal pericardium has not had sufficient time to undergo stretching, compression of the atria, venae cavae and hepatic veins will take place, interfering with the venous return of blood to the heart. Cyanosis, distention of the veins of the neck, fall in arterial pressure and tachycardia are the outstanding features in such instances. Of course, shock associated with sudden rupture may obscure this picture and make the condition undistinguishable from other manifestations of circulatory collapse.

In rupture of the interventricular septum alone the patient may, in occasional instances, survive a long time. One such case where the patient lived five years was reported by Wood and Livezey.[23] Most patients, however, die much earlier, even within hours or days after perforation occurs. The characteristic physical findings are shock and the sudden development of a harsh, loud systolic murmur over the entire precordium with maximum intensity at the third left interspace close to the sternum, frequently associated with a palpable thrill. The heart becomes markedly dilated and evidence

of right ventricular strain develops if the patient survives.

TREATMENT

Inasmuch as rupture of the heart in acute myocardial infarction occurs as a sudden accident and is invariably fatal, treatment is of no avail. With our present knowledge of diagnosis of the condition, we must concentrate on prophylaxis rather than treatment.

It is essential to bear in mind the possibility that rupture of the heart may occur in every case of acute myocardial infarction especially when there is pre-existing and coexisting hypertension, in the older age group and in women. Strict confinement to bed and the avoidance of physical strain and nervous tension are, therefore, called for during the first two weeks of acute infarction or longer if necessary. If there is a drop in pressure not associated with shock, no effort should be made to maintain a normal or higher than normal blood pressure. Drugs are best avoided, except when pain is severe, at which time the opiates or Demerol should be used in sufficient dosage. Dietary care and bowel movement should receive strict supervision. Once rupture has occurred, treatment is usually of no avail. Perhaps surgical interference could conceivably save an occasional life if the condition is recognized early enough and the bleeding is not too rapid. This is particularly true if rupture occurs in an established chronic aneurysm of the heart and where the leak happens to be slow.

In infarction of the interventricular septum with perforation, life may in some cases be prolonged by rest, the use of digitalis and diuretics and other proper symptomatic therapy.

SUMMARY

Rupture of the heart in eight cases of myocardial infarction and a review of the literature are presented. The condition appears to occur more often than the literature would indicate. It affects an area of the heart where fresh myocardial damage is present, but never in areas of organized infarction. In the majority of patients it occurs in the free wall of the left ventricle, mainly in the anterolateral region close to the apex, and may involve portions of the lower interventricular septum. In occasional cases it may affect the interventricular septum alone and rarely it may be confined to the papillary muscle.

One or more of the underlying predisposing causes are pre-existing and coexisting hypertension with its strain on the heart and hypertrophy of the myocardial fiber; the female sex in whom hypertension is more frequent; the older age groups where the normal histologic structure of the myocardium is altered; an early age of the infarct; the effect of leukocytic infiltration with its local enzymatic destructive effect on the myocardium; and the location of the coronary occlusion usually in the anterior descending branch of the left coronary artery. The most important direct cause appears to be an aneurysmal-like expansion of the devitalized myocardium in the area of infarction during systole which produces a suction effect on the blood in that area. This probably causes overdistention and rupture of the arterioluminal and arteriosinusoidal vessels with dissection of blood through the myocardium. Pressure exerted by contraction of the adjacent normal heart muscle upon the devitalized area also causes tearing of the diseased myocardial tissue.

The diagnosis of rupture of the free wall of the heart during life is hard to make but in perforation of the interventricular septum the diagnosis is relatively easy to establish. Treatment of the condition when affecting the free wall should, therefore, be prophylactic. The condition must be borne in mind in any case of myocardial infarction especially when it occurs under the aforementioned circumstances, and careful management of the acute phase of infarction is to be instituted. In perforation of the interventricular septum treatment should be symptomatic and directed toward heart failure.

REFERENCES

1. EDMONDSON, H. A. and HOXIE, H. J. Hypertension and cardiac rupture. Clinical and pathologic study of 72 cases, in 13 of which rupture of interventricular septum occurred. *Am. Heart J.*, 24: 719, 1942.
2. FRIEDMAN, S. and WHITE, P. D. Rupture of the heart in myocardial infarction. Experience in a large general hospital. *Ann. Int. Med.*, 21: 778, 1944.
3. OBLATH, R. W., LEVINSON, D. and GRIFFITH, G. C. Factors influencing rupture of the heart after myocardial infarction. *J. A. M. A.*, 149: 1276, 1952.
4. WESSLER, S., ZOLL, P. M. and SCHLESINGER, M. J. Pathogenesis of spontaneous cardiac rupture. *Circulation*, 6: 334, 1952.
5. MCDONNIEAL, S. H., HUMBRECHT, M. and VOORHIES, N. W. Cardiac rupture. Report of 12 cases from the Southern Baptist Hospital, New Orleans, during a 10 year interval. *J. Louisiana M. Soc.*, 107: 171, 1955.
6. MARTLAND, H. S. Sudden deaths with reference to

their prevention. *Proc. New England Heart A.*, p. 42, 1939–1940.

7. JETTER, W. W. and WHITE, P. D. Rupture of the heart in patients in mental institutions. *Ann. Int. Med.*, 21: 783, 1944.
8. LIPSCHUTZ, E. J. and MALONEY, M. C. Hemopericardium and cardiac tamponade from rupture of heart and aorta. *New York J. Med.*, 23: 3815, 1958.
9. NAREFF, M. J., SKLAR, L. J., KELLY, F. T. and REULING, J. R. Rupture of interventricular septum. *New England J. Med.*, 243: 431, 1950.
10. MALONE, R. G. and PARKES, W. E. Rupture of the interventricular septum. *Brit. Heart J.*, 17: 448, 1955.
11. CRADDOCK, W. L. and MAHE, G. A. Rupture of papillary muscle of heart following myocardial infarction. *J. A. M. A.*, 151: 884, 1953.
12. SIGLER, L. H. The evaluation of claims for workmen's compensation in cardiac disability and death. *Indust. Med.*, 25: 10, 1956.
13. MALAMUD, N. and ZHEUTLIN, A. Fatal cardiac complication during electroshock therapy. *J. Nerv. & Ment. Dis.*, 117: 458, 1953.
14. AARSETH, S. and LANGE, H. F. The influence of anticoagulant therapy on the occurrence of cardiac rupture and hemopericardium following heart infarction. I. A study of 89 cases of hemopericardium. *Am. Heart J.*, 56: 250, 1958.
15. AARSETH, S. and LANGE, H. F. The influence of anticoagulant therapy on the occurrence of cardiac rupture and hemopericardium following heart infarction. II. Controlled study of a selected group based on 1,044 autopsies. *Am. Heart J.*, 56: 257, 1958.
16. COHN, A. E. Disease of the heart. *Science*, 101: 499, 1945.
17. FREEMAN, W. J. Histologic patterns of ruptured myocardial infarcts. *Arch. Path.*, 65: 646, 1958.
18. LUNSETH, J. H. and RUWALDT, M. Pathogenesis of cardiac rupture due to myocardial infarction. *Dis. Chest.*, 30: 499, 1956.
19. MALLORY, G. K., WHITE, P. D. and SALCEDO-SALGAR, J. The speed of healing of myocardial infarction. A study of the pathologic anatomy in seventy-two cases. *Am. Heart J.*, 18: 647, 1939.
20. SUH, S. K. and EDDLEMAN, E. E., JR. Kinetocardiographic findings of myocardial infarction. *Circulation*, 19: 531, 1959.
21. NUZUM, F. R. Auscultatory evidence of cardiac rupture. *Am. Heart J.*, 39: 909, 1950.
22. BISHOP, L. and LOGUE, B. External rupture of the heart causing a systolic murmur and thrill. *J. A. M. A.*, 144: 757, 1950.
23. WOOD, F. C. and LIVEZEY, M. M. Five years survival after perforation of the interventricular septum caused by coronary occlusion. *Am. Heart J.*, 24: 807, 1942.

Disturbances of Rate, Rhythm and Conduction in Acute Myocardial Infarction

A Statistical Study of 153 Cases*

ELIAS S. IMPERIAL, M.D., RODOLFO CARBALLO, M.D. *and* HENRY A. ZIMMERMAN, M.D., F.A.C.C.

Cleveland, Ohio

THIS statistical study of disturbances of rate, rhythm and conduction in the acute phase of myocardial infarction was undertaken to establish relationships between these disturbances and certain facets of the infarction, with particular reference to rate of occurrence, association with the location of the infarct and prognostic significance. The study concerns the analysis of 153 cases of acute myocardial infarction taken from our records within a period of two years. The frequency of disturbances of rate, rhythm and conduction in relation to the entire series is correlated with the location of the infarct, the supervening mechanism or rhythm and the mortality.

Somewhat similar studies have been reported previously, and we have drawn comparisons between their findings and ours. In some of these findings there is a trend to similarity, while in others, we have inferred entirely different conclusions.

PROCEDURES AND MATERIALS

A review of all cases of acute myocardial infarction from the records of St. Vincent Charity Hospital was made covering a two-year period. Diagnosis was based mainly on definite electrocardiographic findings concurrent with elevated SGOT activity. Only those showing anterior (includes all cases of anteroseptal and anterolateral infarctions), diaphragmatic (commonly referred to as "posterior") or combined (anterodiaphragmatic) myocardial infarction were chosen. Cases of dorsal (infarction located in the portion of the left ventricle oriented to the back), subendocardial and intramural infarctions were eliminated from the study as the diagnosis was often debatable and also, these types occurred very rarely. Thus, they were of statistical unimportance. The occurrence of disturbances in rate, rhythm and conduction (proved electrocardiographically) within seventy-two hours after the onset of the infarction was noted; all patients showing any such disturbances prior to the onset of the myocardial infarction were not included in the study. All deaths occurring within the patients' confinement in the hospital were also noted.

The patients were divided into three main groups based on the electrocardiographic locations of the infarct. Each group was then subdivided into the supervening mechanisms (sinus, supraventricular and ventricular) and rhythm, specifying the different irregularities of rate, rhythm and conduction. The percentual incidences of each group and subgroup were computed in relation to the series as a whole, the location of the infarct, the predominant rhythm and predominant mechanisms. The number of deaths was noted in each group and subgroup.

RESULTS

A total of 153 cases were selected on the basis of the criteria mentioned. The distribution is shown in Table I.

Anterior Infarction: The majority of the patients had anterior myocardial infarction with a total of eighty-one patients, accounting for 53 per cent of the whole series. Of these eighty-one patients, sixty-eight (83.9 per cent) had sinus mechanism, eight (9.9 per cent) had supraventricular mechanism and five (6.2 per cent) had ventricular mechanism. Of these eighty-one patients sixty (74 per cent) showed some kind of disturbance in rate, rhythm and/or conduction. The most common disturbance was sinus tachycardia present in twenty-nine patients (35.8 per cent). Other forms of disturbances of rate and rhythm

* From the Marie L. Coakley Cardiovascular Laboratory and Department of Cardiology, St. Vincent Charity Hospital, Cleveland, Ohio.

This study was aided by a grant from the Ashland County Heart Society.

occurred as follows: ventricular premature beats, 14.8 per cent; supraventricular mechanisms, 9.9 per cent; sinus bradycardia, 6.2 per cent; and ventricular tachycardia, 1.2 per cent. Disturbances in conduction occurred in sixteen patients (19.8 per cent), the most common of which was right bundle branch block present in ten patients (12.4 per cent). A-V block was present in six patients or 7.4 per cent. Only twenty-one patients (26 per cent) did not show any disturbance of rate, rhythm and/or conduction.

The total number of deaths in patients with anterior myocardial infarction was twenty-nine (35.7 per cent). In patients showing disturbances of rate, rhythm and/or conduction, the total number of deaths was twenty-eight or a mortality rate of 46.6 per cent. In patients without any disturbance the total number of deaths was only one, or a mortality rate of 4.8 per cent.

Diaphragmatic Infarction: There were sixty patients with diaphragmatic infarction accounting for 39.2 per cent of the whole series. Of these sixty patients, fifty (83.3 per cent) had sinus mechanism, and nine (15 per cent) had supraventricular mechanism. Only one patient (1.7 per cent) had ventricular mechanism (complete A-V block). Forty-four patients showed some form of disturbance in rate, rhythm and/or conduction, accounting for 73.3 per cent of this group. The most common form of disturbance was sinus bradycardia present in seventeen patients (28.3 per cent). Other forms of disturbance in rate and rhythm were supraventricular mechanism present in 15 per cent (all of which were cases of atrial fibrillation, except one of nodal rhythm), sinus tachycardia in 15 per cent and ventricular premature beats in 8.3 per cent. Disturbances in conduction were found in 5 patients (8.4 per cent), the most common of which was A-V block present in four patients, the remaining one having right bundle branch block. Sixteen patients did not show disturbance of any kind or an incidence of 26.7 per cent of the patients with this type of infarction.

The total number of deaths was eighteen or a mortality rate of 30 per cent. In patients showing disturbances of rate, rhythm and/or conduction, the total number of deaths was seventeen, or a mortality rate of 38.6 per cent. In patients having no disturbances, the mortality rate was only 6.3 per cent.

Combined Anterodiaphragmatic Infarction: Twelve patients had combined (anterodiaphragmatic) infarction or an incidence of 7.8 per cent of the whole series. Of these twelve, nine (75 per cent) had sinus mechanism and three (25 per cent) had supraventricular mechanism. Eight patients (66.7 per cent) of this group showed disturbances of rate, rhythm and/or conduction, the most common of which was sinus tachycardia present in four patients (33.3 per cent). Only one patient showed disturbance in conduction (right bundle branch block). There were four patients without any disturbance, accounting for 33.3 per cent of this group. The total number of deaths was six or a mortality rate of 50 per cent. All six deaths occurred among patients with some form of disturbance in rate, rhythm and/or conduction. No deaths occurred in the four patients without disturbance.

The distribution as far as location of the infarct was concerned compares with the usual established incidences, and with the known incidences of involved segments of the coronary circulation[1] supplying the different anatomic aspects of the heart that are the seat of the infarction. This would tend to make any statistical analysis of our series in relation to the location of the infarct sound and significant.

Comments

Disturbances of rate, rhythm and conduction are of very frequent occurrence in the acute phase of myocardial infarction. Scherf[2] claims that cardiac arrhythmias occur in at least 50 per cent of the patients. Ball et al.[3] noted some form of arrhythmias in 67 per cent of their series of 397 patients. Other authors[4-8] have reported varying incidences, from as low as 14.3 per cent when arrhythmias alone are considered, to as high as 98 per cent when disturbances of rate are included. In our series, some form of disturbance in rate, rhythm and/or conduction developed in 112 of 153 patients (73.2 per cent).

There are probably three main factors by which these disturbances are evoked in the acute phase of myocardial infarction: (1) the site and surrounding area of the infarction itself act as a focus of irritability; (2) direct involvement or interference of the blood supply to the conducting system of the heart; and (3) failure of the myocardium as a direct result of the injury.

Disturbances of rate and rhythm are reportedly more common than disturbances of conduction, although the latter have entailed

TABLE I

Distribution of Disturbances of Rate, Rhythm and Conduction in the Different Sites of Acute Myocardial Infarction

Findings	Percentual Incidence in Relation to:					
	Total No. of Cases	Predominant Mechanism	Predominant Rhythm	Location of Infarction	Series as a Whole	Total No. of Deaths
I. Patients with Anterior Myocardial Infarction						
	81				**53.0**	**29**
Sinus mechanism	68	...	...	83.9	44.5	19
Normal sinus rhythm (60–100/min.)	34	50.0	...	41.9	22.2	4
Pure sinus rhythm*	21	30.9	61.8	25.8	13.7	1
Associated with disturbance in rhythm	6	8.8	17.6	7.4	3.9	1
Ventricular premature beats	6	8.8	17.6	7.4	3.9	1
Associated with disturbance in conduction	7	10.3	20.6	8.7	4.6	..
Right bundle branch block	5	7.4	14.7	6.2	3.3	2
Incomplete A-V block	2	2.9	5.9	2.5	1.3	0
Sinus tachycardia (>100/min.)	29	42.6	...	35.8	19.0	15
Pure	18	26.4	62.1	22.2	11.8	9
Associated with disturbance in rhythm	6	8.8	20.7	7.4	3.9	3
Ventricular premature beats	6	8.8	20.7	7.4	3.9	3
Associated with disturbance in conduction	5	7.4	17.2	6.2	3.3	3
Right bundle branch block	5	7.4	17.2	6.2	3.3	3
Sinus bradycardia*	5	7.4	...	6.2	3.3	0
Supraventricular mechanism	8	...	...	9.9	5.2	6
Atrial fibrillation	4	50	...	5.0	2.6	4
Supraventricular tachycardia	2	25	...	2.5	1.3	1
Atrial flutter	1	12.5	...	1.2	0.65	1
Nodal rhythm	1	12.5	...	1.2	0.65	0
Ventricular mechanism	5	...	...	6.2	3.3	5
Complete A-V block with idioventricular rhythm	4	80	...	5.0	2.6	4
Ventricular tachycardia	1	20	...	1.2	0.7	1
II. Patients with Diaphragmatic Infarction						
	60				**39.2**	**18**
Sinus mechanism	50	...	...	83.3	32.6	14
Normal sinus rhythm (60–100/min.)	24	48	...	40.0	15.7	3
Pure sinus rhythm*	16	32	66.6	26.6	10.5	1
Associated with disturbance in rhythm	4	8	16.7	6.7	2.6	1
Ventricular premature beats	4	8	16.7	6.7	2.6	1
Associated with disturbance in conduction	4	8	16.7	6.7	2.6	1
Right bundle branch block	1	2.0	4.2	1.7	0.6	0
Incomplete A-V block	3	6.0	12.5	5.0	2.0	1
Sinus tachycardia (>100/min.)	9	18	...	15.0	5.9	8
Pure	8	16	88.8	13.3	5.2	7
Associated with disturbance in rhythm	1	2	11.2	1.7	0.7	..
Ventricular premature beats	1	2	11.2	1.7	0.7	..
Associated with disturbance in conduction	0	...	...	...	...	..
Sinus bradycardia (<60/min.)*	17	34	...	28.3	11.0	3
Supraventricular mechanism	9	...	...	15.0	5.9	4
Atrial fibrillation	8	88.8	...	13.3	5.2	4
Nodal rhythm	1	11.2	...	1.7	0.7	0
Ventricular mechanism	1	...	...	1.7	0.7	0
Complete A-V block with idioventricular rhythm	1	...	...	1.7	0.7	0

* See footnotes on page 27.

TABLE I (*Continued*)

Findings	Percentual Incidence in Relation to:					
	Total No. of Cases	Predominant Mechanism	Predominant Rhythm	Location of Infarction	Series as a Whole	Total No. of Deaths
III. Patients with Anterodiaphragmatic Infarction (Combined)						
	12				**7.8**	**6**
Sinus mechanism	9	...	...	75	5.8	3
Normal sinus rhythm (60–100/min.)	4	44.4	...	33.3	2.6	..
Pure sinus rhythm*	4	44.4	100	33.3	2.6	0
Associated with disturbance in rhythm	0	...	...	...	...	..
Associated with disturbance in conduction	0	...	...	...	...	..
Sinus tachycardia (>100/min.)	4	44.4	...	33.3	2.6	2
Pure	2	22.2	50	16.65	1.3	1
Associated with disturbance in rhythm	2	22.2	50	16.65	1.3	1
Ventricular premature beats	2	22.2	50	16.65	1.3	1
Associated with disturbance in conduction	0	...	...	...	...	..
Sinus bradycardia (<60/min.)*	1	11.2	...	8.4	0.65	1
Supraventricular mechanism	3	...	...	25.0	2.0	3
Atrial fibrillation	3	100	...	25.0	2.0	3
Pure	2	66.7	66.7	16.6	1.30	2
Associated with disturbance in conduction (right bundle branch block)	1	33.3	33.3	8.4	0.65	1
Ventricular mechanism	0	...	...	...	...	..

NOTE: Figures in bold face type indicate totals in each group.
* Not associated with any disturbance in rhythm or conduction.

a more ominous sign. Of our 153 patients, ninety-six (62.7 per cent) showed some form of disturbance of rate and/or rhythm and twenty-two patients (14.4 per cent) showed some form of disturbance in conduction.

In general, the incidence of these disturbances does not appear to be related to the location of the infarct. In our series there were practically the same percentual incidences of disturbances in patients with different locations of the infarct: 74 per cent for anterior, 73.3 per cent for diaphragmatic and 66.6 per cent for combined (anterodiaphragmatic) infarction, each comparable to the over-all incidence of 73.2 per cent. However, when each disturbance of rate, rhythm and/or conduction is scrutinized, certain types appear distinctly and significantly related to the location of the infarct.

The occurrence of disturbances in acute myocardial infarction is generally agreed to imply a poorer prognosis. Wiggers[9] has pointed out that in the heart with an infarction, which is in the borderline state between efficiency and inefficiency, any irregularity is disadvantageous. With the presence of arrhythmias an increase of 6.6 per cent in the mortality rate was found by Johnson and Miner[6] in their study of 187 patients while Rosenbaum and Levine[10] found an increase of 15 per cent in their study of 372 patients. In our series, the total number of deaths was fifty-three or a mortality rate of 34.6 per cent. On the other hand, when patients with some form of disturbance are considered, the mortality rate increased to 45.5 per cent (fifty-one deaths among 112 patients). Again, certain types of disturbances present a more despondent prognosis than others.

The following is an analysis of the different disturbances or rate, rhythm and conduction with particular reference to our own study.

DISTURBANCES OF RATE AND RHYTHM

Sinus Tachycardia. The incidence of sinus tachycardia in patients with acute myocardial infarction has been reported to be as high as 98 per cent.[8] In our series, we found it to be present in only 27.5 per cent. It represented the most common form of disturbance in patients

with anterior myocardial and combined type of infarction, with an incidence of 35.8 per cent and 33.3 per cent respectively, whereas it was found in only 15 per cent of patients with diaphragmatic infarction. The mortality rate for this type of disturbance was over 50 per cent in both anterior and combined type of infarctions, and was 88.8 per cent in patients with pure diaphragmatic infarction, as compared to the over-all mortality rate of 34.6 per cent. Wood and Barnes[11] likewise noted a doubling of the mortality rate whenever marked sinus tachycardia occurred, indicating a serious prognosis whenever this disturbance was found in the acute phase of myocardial infarction.

Sinus Bradycardia: Sinus bradycardia was present in 14.9 per cent of the whole series, and in 11 per cent of patients with acute diaphragmatic infarction, being the most common disturbance in the latter (28.3 per cent of the patients). It was rare in the anterior (6.2 per cent of the patients) and the combined (8.4 per cent of the patients) types of infarction. One may infer that the chance that sinus bradycardia will occur in association with acute diaphragmatic infarction is over 75 per cent. There were four deaths among patients with this type of disturbance or a mortality rate of 17.4 per cent, far below the mortality rate of the whole series, indicating a more optimistic outlook than the other disturbances.

Ventricular Premature Beats: This type of disturbance was found in 12.4 per cent of the whole series and represents the most common form of disturbance of rhythm. They were equally common in anterior, diaphragmatic and combined infarctions. There were seven deaths or a mortality of 36.8 per cent in this group. Four of these deaths, however, were in patients who had concomitant sinus tachycardia, which would tend to lower the mortality if ventricular premature beats alone were considered. In our opinion this type of disturbance does not constitute a grave prognostic sign unless it occurs frequently or multifocally.

Atrial Fibrillation: Fifteen patients (9.8 per cent) showed atrial fibrillation in our entire series. This incidence is comparable to the incidence of 7.7 per cent reported by Askey[12] in a study of 1,024 cases. It was the most common type of ectopic mechanism in all three types (anterior, diaphragmatic and combined infarction), although, by comparison on the basis of percentual incidence, it occurred at a higher rate of frequency in the combined (25 per cent of patients) and diaphragmatic (13.3 per cent of patients) types. It was associated with a much higher mortality rate (73.8 per cent) than the whole series, constituting a dire prognostic sign.

Supraventricular Tachycardia: There were only two patients (1.3 per cent of the whole series) with this type of disturbance and both had an anterior infarction. Of the two, one died.

Nodal Rhythm: Two patients (1.3 per cent of the whole series) were found to have this disturbance: one had an anterior and the other a diaphragmatic infarction. Both patients survived.

Atrial Flutter: We found only one case of atrial flutter and this occurred in a patient with anterior infarction. This patient died.

Ventricular Tachycardia and Fibrillation: Although this disturbance has been suspected as actually occurring more frequently than proved and implicated as an immediate cause for death in a large number of patients in the acute phase of myocardial infarction, our study shows only one such case with electrocardiographic evidence. This occurred in a patient who suffered a fatal anterior infarction.

DISTURBANCES IN CONDUCTION

Bundle Branch Block: All our cases of bundle branch block were of right bundle branch block which was present in twelve patients or a total incidence of 7.8 per cent. Of these twelve, ten had anterior myocardial infarction, all specifically anteroseptal. One patient had diaphragmatic and the other had a combined type of infarction, the latter in conjunction with atrial fibrillation. It represented the most common form of disturbance of conduction in anterior infarction and in the entire series and signifies a relationship to septal involvement. Half of the patients with this disturbance died.

Although left bundle branch block has been described as one of the complications of acute myocardial infarction, proving the latter in the presence of this type of electrocardiographic disturbance is possible in only a few cases, the majority being discovered by autopsy. Prognosis in the presence of this disturbance in acute myocardial infarction is probably worse than in right bundle branch block.

A-V Block: There were ten patients (6.6 per cent) with A-V block in the whole series, half of which were of the incomplete and the other half of the complete type. Master et al.[13] and Goldman[14] have associated this disturbance mainly with the posterior (dia-

phragmatic) type of infarction. Of our ten patients, however, six had anterior infarction, four of whom had complete A-V block. The other four had diaphragmatic infarction and only one showed complete A-V block. By way of percentual incidence, however, A-V block occurred in practically the same frequency in both the anterior (7.5 per cent of patients) and diaphragmatic (6.7 per cent of patients) type of infarction, although in the latter it represented the most common form of disturbance in conduction. From our study we cannot show any correlation between this type of disturbance and the location of the infarct. The mortality rate (one death among five patients or 20 per cent) with incomplete A-V block was lower than the over-all mortality rate, whereas, in cases of complete A-V block, it was much higher (four deaths in five patients or 80 per cent).

PROGNOSTIC SIGNIFICANCE OF ARRHYTHMIAS

In spite of the high incidence of disturbances in rate, rhythm and conduction in our series, it should be pointed out that sinus mechanism was predominant in all three types of infarction, ectopic mechanisms being present in no more than 20 to 30 per cent. The high mortality, particularly of certain types of disturbances, invokes mandatory and early treatment.

Of the 26.8 per cent (forty-one patients) of the whole series who did not show any type of disturbance (pure sinus rhythm), there were only two deaths or a mortality rate of 4.9 per cent, a ratio of 1 : 8 deaths when compared to the over-all mortality of the entire series. This finding in the presence of acute myocardial infarction undoubtedly signifies good prognosis.

We leave it to the reader to evaluate our findings for their statistical worth, bearing in mind that statistics should always be looked upon as being the effect of a cause and should not be considered as a cause by themselves. In many instances it may be a contributory factor in making a diagnosis using certain established relationships beyond mathematical chance, and yet should never be the main basis for diagnosis. It should be used as an index to suspicion rather than to judgment. Its main importance lies in the realms of prediction, thus its value in prognosis.

Summary and Conclusions

1. An analysis of 153 patients with acute myocardial infarction showed some form of disturbance in rate, rhythm and conduction in 73.2 per cent.

2. The mortality rate of the patients in general with some form of disturbance was considerably higher than the over-all mortality rate.

3. Correlation between certain types of disturbances and location of the infarct was established.

4. The mortality rate significantly varied with different types of disturbances but not with different locations of the infarct.

5. Prognosis in acute myocardial infarction can be judiciously based on evaluation of the cardiac rhythm.

References

1. Luisada, A. A. Heart, 2nd ed. Baltimore, 1954. Williams & Wilkins.
2. Scherf, D. Treatment of arrhythmias in myocardial infarction. *Am. J. Cardiol.*, 1: 242, 1958.
3. Ball, C. O. T., Billings, T. F., Jr., Furman, R. H., Brothers, G. B., Thomas, J. C., Aus, M. C. and Meneely, G. R. The functional circulatory consequences of myocardial infarction. *Circulation*, 11: 749, 1955.
4. Master, A. M., Dack, S. and Jaffe, H. L. Disturbances of rate and rhythm in acute coronary artery thrombosis. *Ann. Int. Med.*, 11: 735, 1937.
5. Sambhi, M. P. and Zimmerman, H. A. Acute myocardial infarction. *Ohio M. J.*, 52: 718, 1958.
6. Johnson, C. C. and Miner, F. P. The occurrence of arrhythmias in acute myocardial infarctions. *Dis. Chest*, 33: 414, 1958.
7. Smith, J. F., Keyes, W. J. and Denham, M. R. Myocardial infarction. A study of the acute phase in 920 patients. *Am. J. M. Sc.*, 221: 508, 1951.
8. Shillito, F. H., Chamberlain, F. L. and Levy, R. L. Cardiac infarction. *J. A. M. A.*, 118: 779, 1942.
9. Wiggers, C. J. The functional consequences of coronary occlusion. *Ann. Int. Med.*, 23: 158, 1945.
10. Rosenbaum, F. F. and Levine, S. A. The prognostic value of various clinical and electrocardiographic features of acute myocardial infarction. I. Immediate prognosis. *Arch. Int. Med.*, 68: 913, 1941.
11. Wood, R. M. and Barnes, A. R. Factors influencing immediate mortality after acute coronary occlusion. *Am. Heart J.*, 24: 4, 1942.
12. Askey, J. M. Auricular flutter in association with myocardial infarction. *Am. J. Med.*, 6: 453, 1949.
13. Master, A. M., Dack S. and Jaffe, H. L. Partial and complete heart block in acute coronary occlusion. *Am. J. M. Sc.*, 196: 513, 1938.
14. Goldman, M. J. Cardiac arrhythmias in myocardial infarction. *Am. Heart J.*, 38: 984, 1950.

Thumping of the Precordium in Ventricular Standstill*

DAVID SCHERF, M.D., F.A.C.C. *and* CARL BORNEMANN, M.D.

New York, New York

RARELY does a greater medical emergency arise than ventricular standstill. In a recent analysis of the cause of death in a series of 250 patients with healed myocardial infarction, 40.8 per cent died suddenly because, in the absence of congestive failure or a new infarction, presumably ventricular standstill or fibrillation occurred.[1,2,4] Not only is ventricular standstill the immediate cause of death but it is also a major cause of Morgagni-Stokes-Adams attacks. With the increase of intrathoracic surgery in recent years, ventricular standstill during opening of the pleura or the pericardium or manipulation of the heart is encountered with increasing frequency. In all these emergencies the heart muscle may be sufficiently intact to sustain life if an effective means of therapy can be promptly employed.

Most articles and textbooks dealing with this emergency mention a simple method of treatment; viz., thumping the precordium. Blows with the fist to the precordium of the intact chest wall or with a blunt instrument to the surface of the exposed heart will lead to one or more contractions and may restore automaticity. Experience shows, however, that this simple and often effective method is too little known. Precious time elapses after the onset of standstill while intracardiac injections are prepared or the artificial pacemaker is applied at the bedside. In this context those who still favor intracardiac injections should not forget that the mechanical stimulus of the needle penetrating the heart may suffice to restore automaticity while the injected substance (epinephrine is frequently recommended) may lead to the appearance of ventricular fibrillation.

The purpose of the present report is to demonstrate the effectiveness of mechanical stimulation of the heart in the management of cardiac resuscitation. Electrocardiograms have been obtained from eleven patients during ventricular standstill and when blows to the precordium have elicited automatic ectopic beats (Table I). The clinical tracings will be compared with experimental tracings on dogs. The resulting arrhythmias will be analyzed.

CASE REPORTS

CASE 1. L. C., a fifty-three year old man, presented the clinical and electrocardiographic picture of an acute myocardial infarction of the inferior wall complicated by severe retrosternal pain unrelieved by morphine, vomiting, shock without loss of consciousness, and shift from normal sinus rhythm to complete A-V block. During an infusion of norepinephrine (Levophed®) and cortisone the blood pressure rose to preshock levels of 110/60 mm. Hg. Shortly afterwards cardiac standstill intervened. For one hour, ventricular systole could be established temporarily only by pounding the chest wall over the precordium. Eventually automatic ventricular rhythm was re-established by the intravenous injection of isoproterenol (Isuprel®).

On the following morning the heart sounds became very distant, the blood pressure unobtainable and attacks of dizziness, convulsions, pallor and profuse sweating occurred as the electrocardiogram recorded periods of complete ventricular standstill. While an intravenous infusion of Levophed was being prepared the heart action was maintained by blows applied to the precordium. Figure 1A shows a slow, irregular atrial activity and two automatic ventricular beats arising in different foci. Pounding the precordium (arrow) produced two ventricular contractions in quick succession followed by a rapid ventricular automatism which quickly slowed and never included more than nine beats. Whenever the precordium was struck a rapid and subsequent slow automatism appeared, the latter originating in a different center (Fig. 1B).

Sixty-four hours after admission pounding elicited almost monophasic ventricular complexes (Fig. 1C). Complete cardiac standstill obtained during the

* From the Department of Medicine, New York Medical College, New York, New York.

TABLE I
Summary of Eleven Cases of Ventricular Standstill

Case	Age (yr.)	Diagnosis	Results of Thumping
1, L. C.	53	Inferior wall infarction with complete A-V block	Life prolonged by blows applied for one hour, maintaining ventricular systole until automatism re-established
2, M. L.	78	Hypertension, complete A-V block with Morgagni-Stokes-Adams attacks caused by ventricular tachycardia and ventricular fibrillation	Life preserved by blows during asystole establishing a ventricular automatism
3, E. H. G.	71	Systolic hypertension, complete A-V block and Morgagni-Stokes-Adams attacks caused by short runs of ventricular tachycardia	Life preserved on two occasions with one resuscitation several minutes after onset of apnea and death-like pallor
4, M. S.	79	Acute myocardial infarction of inferior wall; A-V block terminating in standstill	At time of death during standstill pounding repeatedly awakened automatism of ventricular center
5, J. B.	76	Shock precipitated by pulmonary embolism, ventricular automatism with shifting pacemaker terminating in standstill	Pounding of a dying heart in standstill produced a regular ventricular tachycardia followed by a slow automatism in absence of atrial activity
6, R. L. P.	66	Trachetomized patient died in respiratory decompensation secondary to lymphocytic lymphosarcoma with widespread metastasis; electrocardiogram essentially normal antemortem; at death a slow ventricular automaticity developed	Thumping during slow ventricular automaticity produced other ectopic rhythms with a more rapid rate and of prolonged duration, terminating in standstill preceded once by ventricular fibrillation; pounding eventually gave way to bigeminal beats
7, M. B. R.	81	Inactive tuberculosis, chronic constrictive pericarditis with calcification, chronic cardiac failure with cardiac fibrosis of liver, terminal atrial tachycardia ending in standstill	Blows to chest elicited a ventricular automatic beat followed by ectopic tachycardia arising in a distant focus
8, W. A. C.	69	Dissection of the aorta with cardiac tamponade; cardiac activity exhibited successively slow ventricular ectopic rhythm, ventricular flutter and fibrillation, succeeded by ventricular standstill	Blows, at death, elicited pairs of beats and eventually an ectopic rhythm
9, L. A.	76	Acute infarction of anterolateral wall with ventricular standstill	Blows to chest produced successive ectopic beats, leading to a series of automatic beats, ventricular flutter and fibrillation with a series of ectopic beats again elicited after standstill
10, E. H. S.	80	Acute myocardial infarction of anterior wall complicated by diabetes and carcinoma of ureter, left bundle branch block with ventricular extrasystoles, ectopic ventricular rhythm, ventricular fibrillation and standstill	Thumping failed to alter pattern of ventricular fibrillation or re-establish ventricular rhythm after standstill
11, M. T.	71	Acute myocardial infarction and standstill	Six blows produced a series of 26 beats; standstill with more blows eliciting a series of 61 beats; standstill lasting forty-two seconds before 22 blows over a thirty-second period reawakened an ectopic center resulting in a series of beats; this was repeated several times

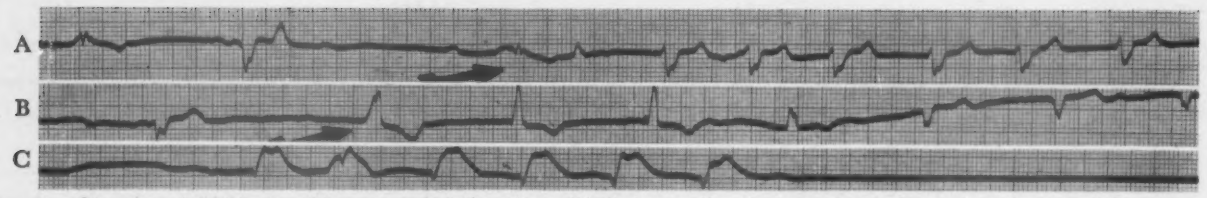


FIG. 1. Case 1. A-V block with an acute infarction of inferior wall. A, irregularly formed and spaced P waves appear and two automatic ventricular beats are visible at the beginning of the tracing. Pounding of the precordium (arrow) produces 2 ventricular contractions in quick succession and a series of ventricular beats follows, arising in another center and with a slowly declining rate. B, a similar effect of pounding the chest. C, the effect of pounding the chest shortly before death; again a series of ectopic beats follows with almost monophasic ventricular complexes.

intervals between thumping. Finally the blows to the precordium failed to awaken automatism.

Comment: This observation demonstrates that a patient could be kept alive for one hour by blows to the precordium until automatism was established. On the next day the method was only temporarily effective as the condition of the heart deteriorated. This observation further illustrates a phenomenon which we have observed repeatedly in other patients; namely, automatism is awakened in a center distant from the one initially stimulated by the blows. Mechanical stimulation of the heart leads to a spread of an excitation wave over the ventricles which initiates the automatism of another center. This automatism may slow down and disappear after the formation of a few impulses or may persist.

CASE 2. M. L., a seventy-eight year old woman, was readmitted because of Morgagni-Stokes-Adams attacks with periods of unconsciousness accompanied by convulsions. On a previous admission for osteoarthritis, left ventricular enlargement, a blood pressure of 200/98 mm. Hg, a harsh systolic murmur in the aortic area and an A-V block were noted. On this admission the electrocardiograms recorded during several attacks disclosed essentially identical changes of rhythm (Fig. 2). The abrupt onset of a ventricular tachycardia with variform ventricular complexes would be followed by a short burst of ventricular fibrillation (Fig. 2B). This would end with a series of ventricular extrasystoles terminated by ventricular standstill. Thumping of the chest wall, as indicated by the arrows, elicited single ectopic beats until a ventricular automatism appeared spontaneously. This same pattern would be repeated every few minutes until the attacks ceased. Once free of the attacks, the patient signed out but several weeks later she succumbed at another hospital with the same condition.

Comment: As in this patient, Morgagni-Stokes-Adams attacks in the presence of a complete A-V block are often caused by ventricular tachycardia and fibrillation. Ventricular standstill follows such a tachycardia because the rapid cardiac action leads to a "fatigue" phenomenon of the ventricular centers. The more damaged the centers are, the longer the standstill.[2] Standstill following ventricular tachycardia and fibrillation, if prolonged, dangerously compromises the circulation. In

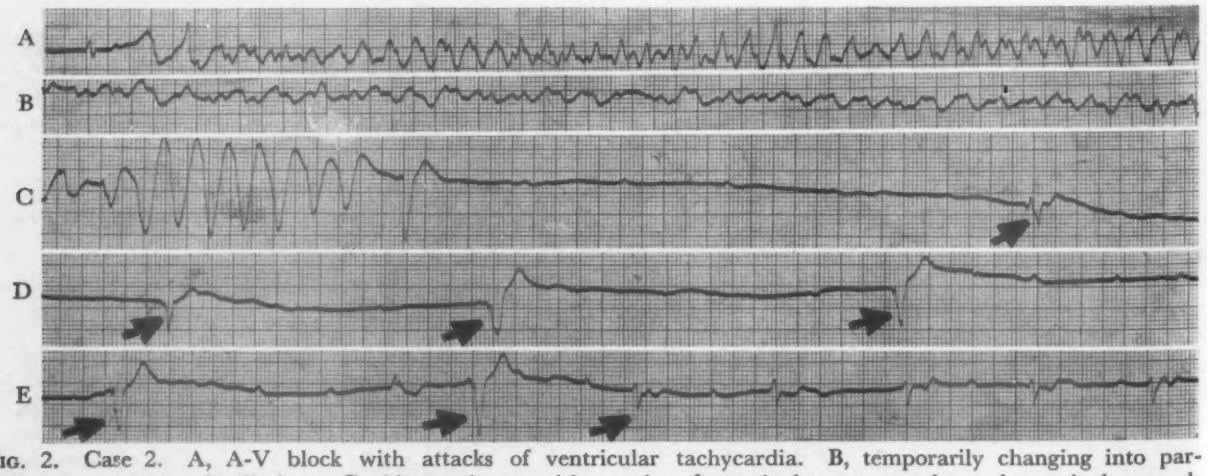


FIG. 2. Case 2. A, A-V block with attacks of ventricular tachycardia. B, temporarily changing into paroxysmal ventricular fibrillation. C, this terminates with a series of ventricular extrasystoles and ventricular standstill follows. C, D and E, thumping the chest always leads to appearance of single ventricular contractions. E, finally spontaneous automatism reappears.

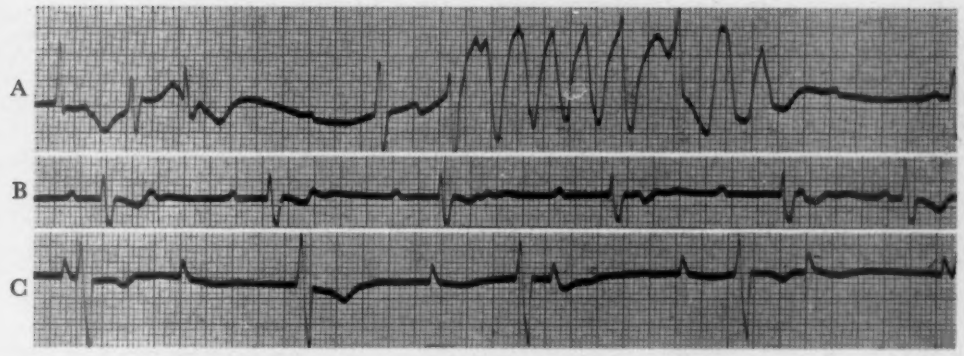


FIG. 3. Case 3. A, short runs of ventricular extrasystoles originating in different centers appeared with heart block caused by coronary sclerosis. B, usually a complete A-V block prevailed, but occasionally a sinus beat was conducted to the ventricles (last beat). C, after a prolonged attack of the Morgagni-Stokes-Adams syndrome which was immediately terminated by application of sharp blows toward the precordium demonstrating again complete A-V block.

this patient, this was avoided by blows to the chest wall which initiated automatic beats and awakened a spontaneous automatism.

CASE 3. E. H. G., a seventy-one year old retired college professor, died suddenly in the fifth of a series of Morgagni-Stokes-Adams attacks which had occurred within a three-week period. Four years previously his systolic blood pressure was 200 mm. and the electrocardiogram revealed bundle branch block with a 2 : 1 A-V block. His two initial attacks of "black outs" shortly followed the institution of digitalis therapy. The third attack took place when he was awaiting a visit from one of us. He breathed stertorously and his arms performed slight clonic movements. Within a few moments after the delivery of several sharp blows to the precordium, he regained consciousness. Subsequent electrocardiograms exhibited a complete A-V block and short runs of ventricular tachycardia coinciding with a subjective sensation of a "surge, in and out of the head" and incipient faintness (Fig. 3A). Occasionally as illustrated by the last beat in Fig. 3B (lead I) an atrial impulse successfully reached the ventricle.

The fourth attack occurred as the patient was in bed conversing with his room mate. He suddenly became silent. Several minutes later an attendant responded to the room mate's frantic signals. The patient was apneic, pulseless, cold and exhibited the grey-pallor of death. One or two sharp blows over the precordium almost immediately established a pulse. The face became suffused with blood and respirations began. An electrocardiogram was recorded immediately, revealing an A-V block (Fig. 3C). As oxygen was given by mask, body movements gradually reappeared. The blood pressure, which before the attack had been 280/70, was 230/130 and fell within a few hours to 130/70 mm. Hg. The patient's memory and speech recovered after several hours without evidence of a mental deficit or neurologic disturbance. He died about thirty-six hours later in a similar attack when blows to the chest failed to revive him.

Comment: This patient, before succumbing to the syndrome, survived a prolonged Morgagni-

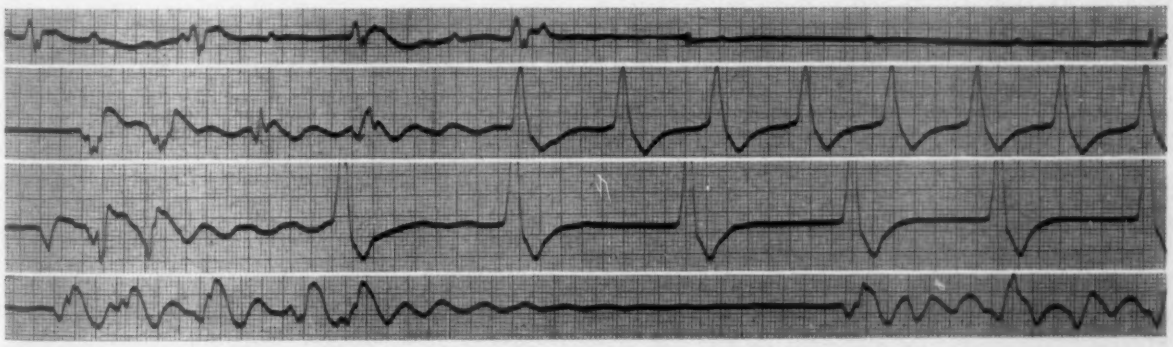


FIG. 4. Case 4. A, the first part shows complete A-V block with elevated RS-T segments due to an acute myocardial infarction; the second part shows ventricular standstill. B, pounding of the chest in the precordial area leads to the appearance of ectopic beats followed by a regular ectopic rhythm, originating in another center. C, this ectopic rhythm slowed down gradually but could be repeatedly reawakened by the same method. The rate of the ectopic rhythm gradually became slower and the ventricular complexes became more bizarre. D, the undulating round waves in these portions of the figure are attributed to partial slow ventricular activations.

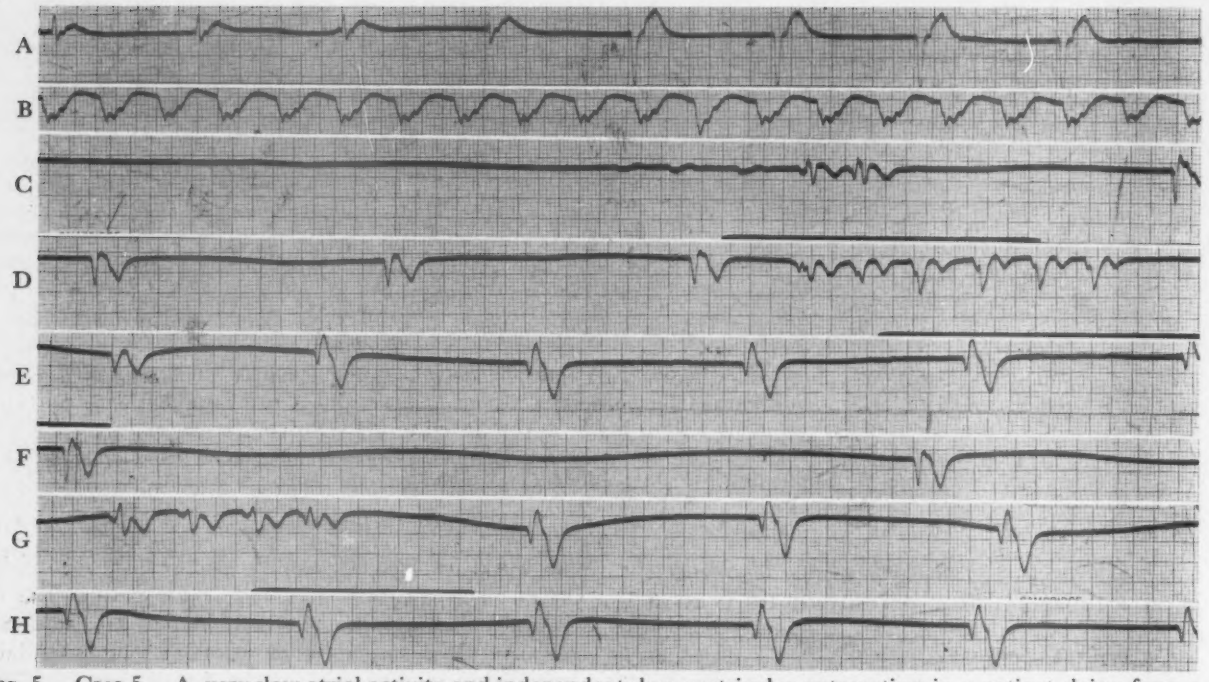


FIG. 5. Case 5. A, very slow atrial activity and independent slow ventricular automatism in a patient dying from a pulmonary embolism. B, blows to the precordium caused a rapid ventricular tachycardia. C, repeated blows to the precordium, indicated in some tracings by the horizontal black lines caused a series of fast ectopic beats which in return elicited a slow automatism in another center (D-H). D and E, these are continuous tracings.

Stokes-Adams attack with a dramatic response to the application of blows to the precordium. The mechanism of this attack may be presumed to have been ventricular standstill since restitution of cardiac activity promptly followed the delivery of the blows. Blows during the terminal episode proved to be ineffectual, possibly because ventricular fibrillation rather than standstill prevailed. An autopsy disclosed myocardial fibrosis without evidence of infarction.

CASE 4. Mrs. M. S., a seventy-nine year old woman, died about sixty-one hours after the onset of a severe retrosternal pain. A continuous levarterenol bitartrate infusion to combat shock was administered during the last fourteen hours of life. A few hours before death the electrocardiogram showed a pattern of infarction of the inferior wall with a complete A-V block (Fig. 4A). Suddenly, during the recording of the electrocardiogram, cardiac standstill appeared (second part of Fig. 4A). Pounding the chest (Fig. 4B) led to the appearance of bizarre ventricular complexes and low round waves which suggested a ventricular flutter with a slow rate; this reawakened a ventricular center which formed impulses rapidly at first and then slowly (Fig. 4C). Renewed pounding led again to automaticity but with a slower rate. Gradually the automaticity of the ventricular center slowed more until only a series of bizarre complexes with flutter waves appeared (Fig. 4D).

Comment: This observation illustrates the efficacy of blows to the precordium in awakening the automatism of a distant center.

CASE 5. J. B., a seventy-six year old woman without a known cardiac history, but with clinical signs of chronic venous stasis involving her left leg, suddenly went into shock while sitting by her bedside. She died within three quarters of an hour without regaining consciousness. Death was attributed to a pulmonary embolus, later confirmed at autopsy.

During this attack the electrocardiogram (Fig. 5A) showed a ventricular automatism with slow, irregularly formed P waves. Next, when cardiac standstill appeared, blows to the precordium evoked a regular ventricular tachycardia which suddenly terminated after 134 beats (Fig. 5B). Subsequently only blows to the chest wall could awaken spontaneous activity of the ventricular centers which at first originated a sequence of rapid impulses, soon changing to a slow rhythm. The automatic ventricular complexes became progressively widened. Finally, blows to the precordial area failed to elicit a response.

Comment: Automatism following mechanical stimulation of the heart by blows to the chest is of longer duration in this patient and the following one than in our other patients with primary cardiac disease. In this patient it is of further interest that pounding led to the ap-

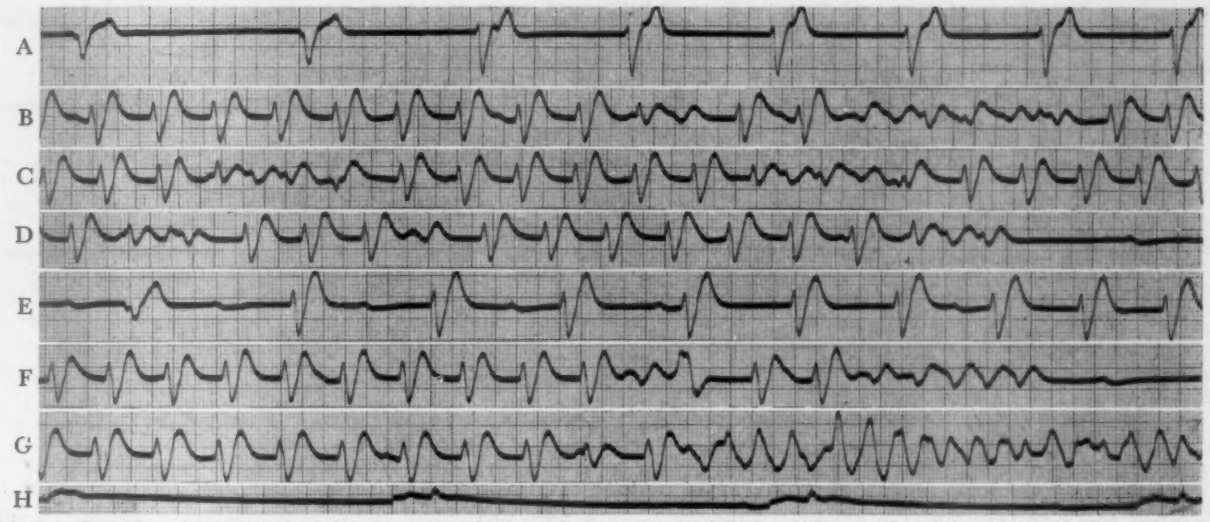


FIG. 6. Case 6. A, a patient dying because of a lymphosarcoma had little evidence of atrial activity in the electrocardiogram and a slow ventricular rhythm. B, blows to the chest wall led to a faster ectopic rhythm which gradually increased in rate. B, C and D, occasionally bizarre tracings appeared, attributed to short bouts of ventricular fibrillation. After the end of the series of ectopic beats, ventricular standstill appeared (end of D). E and F, pounding of the precordial area again elicited a ventricular ectopic rhythm with increasing rate. G, finally ventricular fibrillation appeared. H, after this had subsided pounding caused a bigeminal rhythm.

pearance of automatic ventricular contractions at a time when no evidence of atrial activity could be detected.

CASE 6. Mr. R. L. P., sixty-six year old normotensive and noncardiac patient, died three weeks after a tracheotomy had been performed to relieve a respiratory obstruction above the level of the upper trachea due to the encroachment of a lymphocytic lymphosarcoma upon the pharynx. Accumulation of secretions in the tracheobronchial tree, extramural pressure on both major bronchi by tumor masses at the carina and neoplastic infiltration of both lower lungs led to an inevitably fatal respiratory decompensation. A half hour before respirations ceased an electrocardiogram was essentially normal, although it indicated right axis deviation. As hypoxemia developed and plasma carbon dioxide content presumably increased, the blood pressure rose to 190/90 mm. Hg ten minutes before death.

During these terminal obstructive manifestations a continuous electrocardiographic recording disclosed a slow ventricular automaticity with little evidence of atrial activity. Blows to the chest wall over the heart awakened another center leading to an increased rate of automatism (Fig. 6A). This series of rapid ventricular beats containing about 540 complexes was interrupted by brief sequences of bizarre complexes assumed to be short bouts of ventricular fibrillation (Fig. 6B, 6C and 6D). When standstill followed, pounding over the precordium initiated a rapid ventricular rhythm encompassing 82 beats. A third series, similarly provoked, totaled 158 beats. In Figure 6E, we see the onset of a slow rhythm after a few blows followed by the development of an increased rate terminating in a ventricular flutter (Fig. 6F). A fourth series, also evoked by pounding, consisted of 93 ectopic beats. Finally, thumping the chest produced a succession of 36 automatic beats giving way to ventricular fibrillation (Fig. 6G). After persisting for several minutes, fibrillation yielded to standstill. Blows to the precordium then elicited the complexes seen in Figure 6H, which we interpret as a bigeminy occurring under conditions imposed by the great hypoxia now prevailing in the ventricular muscle.

Comment: The microscopic sections of this patient's autopsy material showed marked perivascular infiltration or "collaring" by lymphocytes about moderately arteriosclerotic coronary vessels, but no significant myocardial damage. Thus, the relatively little damaged ventricles were able to respond to the stimulus of blows to the precordium with prolonged periods of automatism. With increased hypoxia, a depressed automatism set in replaced by the bigeminal rhythm noted terminally.

CASE 7. M. B. R., an eighty-one year old man with marked kyphoscoliosis, died forty-one days after a syncopal attack associated with massive T wave inversion in leads I, II, aVL and chest leads which almost returned to the isoelectric line within twenty-one days. Past history included Potts disease at the age of seven; a myocardial infarction of the posterior wall at the age of seventy; atrial fibrillation and signs of chronic congestive heart failure predominantly right-sided with persistent small bilateral pleural effusions, since seventy-three years of age. Edema progressed to anasarca and death occurred eleven hours after onset of pulmonary edema

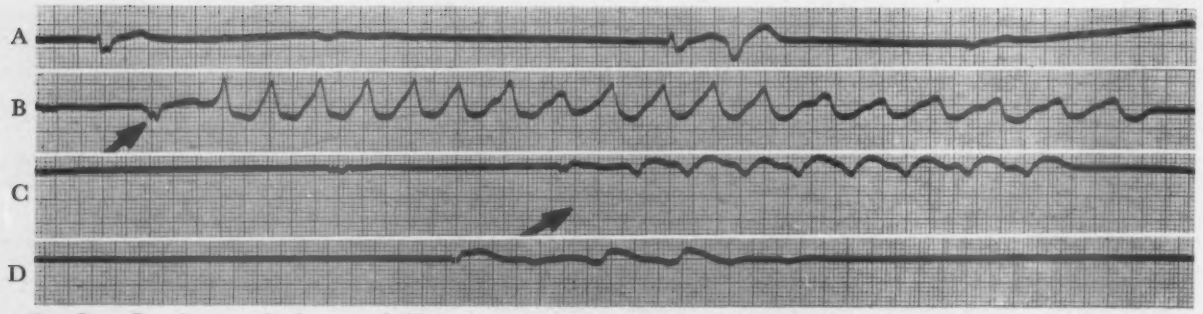


FIG. 7. Case 7. A, ventricular standstill in a patient with coronary sclerosis and a history of an old myocardial infarction. B, C and D, pounding of the precordial area led to a single automatic beat, followed by a ventricular tachycardia originating in a different center. Gradually evidence of increasing hypoxia of the myocardium appeared.

and semicoma. One hour before death an electrocardiogram exhibited an atrial tachycardia with an A-V block and positive T waves.

Five minutes after respirations ceased the electrocardiogram registered ventricular standstill. Thumping the chest wall produced single ventricular automatic beats (Fig. 7A) eventually establishing an ectopic tachycardia with a rate of 150 (Fig. 7B). Brief runs of ectopic tachycardias were repeatedly caused in this fashion until the ventricular complexes (Figs. 7C and 7D) showed evidence of marked hypoxia of the ventricles.

Comment: Postmortem examination revealed pericardial adhesions with calcification, bilateral hydrothorax, diffuse myocardial fibrosis, cardiac fibrosis of liver and healed tuberculous infection of spine, lungs and tracheobronchial lymph nodes. The limited response in this patient to mechanical stimulation could be anticipated by the marked degree of the pathologic changes present at autopsy and by the chronic clinical course. As has been noted in our other cases blows to the chest, nevertheless, formed automatic beats followed by a ventricular tachycardia arising in a distant center. Severe deterioration in the condition of the heart precluded the securing of a sustained response.

CASE 8. Mr. W. A. C., aged sixty-nine, a motor mechanic with mild essential hypertension, suddenly experienced a severe constricting pain encircling the lower part of his chest and the upper part of his abdomen. Three days later, because of persistent discomfort, vomiting, retching and marked restlessness, he was admitted to the hospital. Blood pressure fluctuated between 190/100 and 160/80 mm. Hg; there was a moderate leukocytosis with a shift to the left, and an electrocardiogram was essentially normal although a tall R wave in lead V_4 was compatible with left ventricular hypertrophy. His pain shifted slightly to the left side of the abdomen. Four and a half days after the onset, he suddenly went into shock, stated he was paralyzed and lost consciousness. The neck veins were markedly distended, pupils unequal and fingernail prints could be made out on the skin overlying the right parasternal region, which had resulted from agonal clutching. Percussion of flatness over the precordium was precluded by emphysema.

An electrocardiogram, at this time, revealed a complete atrial standstill associated with a slow ventricular ectopic rhythm which was supplanted by a rhythm originating from a different center with an increased rate. This gave way to ventricular flutter and fibrillation. Within two minutes, the latter terminated in standstill.

Blows applied to the chest repeatedly elicited pairs of beats with a low voltage and a monophasic curve. After eight blows an ectopic rhythm was established lasting about one minute before standstill recurred. Blows subsequently produced single beats of low voltage terminating in an ectopic rhythm lasting about one half a minute. Finally, only single pairs of coupled beats were elicited.

Comment: This observation shows that automatism may be aroused by blows to the chest wall during standstill following ventricular fibrillation. Autopsy disclosed a dissection of the aorta, with rupture into the pericardium producing tamponade and intimal tears in the arch and above the iliac bifurcation.

CASE 9. This seventy-six year old woman died within a few hours after the onset of severe retrosternal pain, associated with a myocardial infarction of the acute anterolateral wall. For ten years preceding her admission she required five to ten tablets of nitroglycerin daily for angina pectoris. On admission, shock obtained and the administration of Demerol® failed to relieve her pain. While an infusion of levarterenol bitartrate was being prepared, the patient was given an injection of 30 mg. of mephentermine (Wyamine®) immediately. A few minutes later, during the recording of an electrocardiogram, ventricular standstill suddenly appeared with very rare P waves.

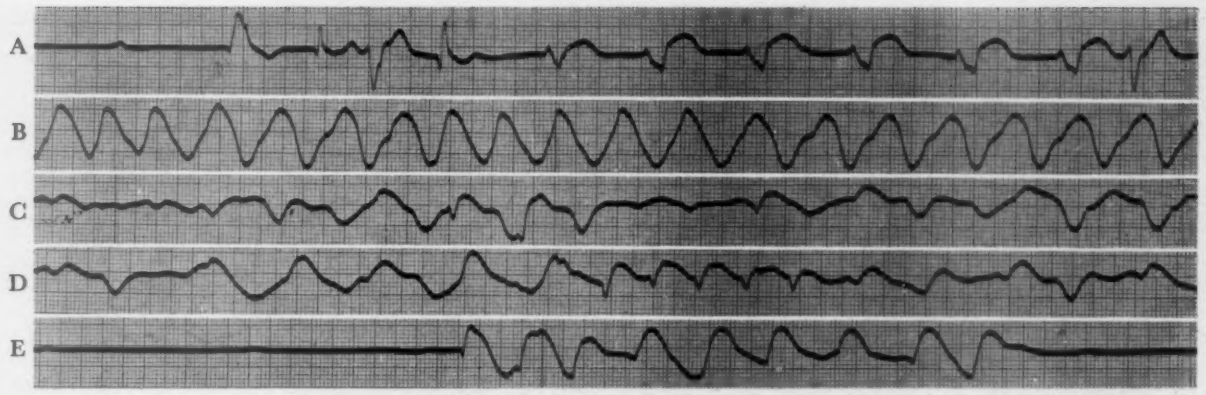


FIG. 8. Case 9. A patient with an acute anterolateral infarction and ventricular standstill. A, blows to the precordial area led to the appearance of a few multifocal beats and a regular automatism followed. B, this is followed by a ventricular tachycardia with wide complexes resembling ventricular flutter. C and D, following this a tracing resembling ventricular fibrillation appeared but pounding led to a series of regular ectopic beats. E, very wide and sluggish ventricular complexes, again elicited terminally by pounding the precordium.

Blows to the precordium in rapid succession caused several ectopic beats (Fig. 8A) followed by a series of automatic beats spaced at fairly regular intervals. These beats gradually changed into wide ventricular complexes which, as in flutter, do not permit separation of the QRS complex and T wave (Fig. 8B). Even when a disturbance suggesting ventricular fibrillation developed (beginning of Fig. 8C), blows to the chest twice elicited a few regular complexes (Fig. 8D). During the succeeding period of ventricular standstill, striking the precordium repeatedly initiated a series of ectopic beats (Fig. 8E). A few minutes later no response could be elicited.

Comment: This observation suggests that blows to the chest may not only establish ventricular automatism during standstill preceding and following ventricular fibrillation, but may also provoke a coordinated heart action during the presence of an electrocardiogram suggesting ventricular fibrillation.

CASE 10. E. H. S., an eighty year old obese clergyman with diabetes, mild hypertension, congestive failure and an epithelioma of the left ureter metastatic to the lungs, liver, retroperitoneal and tracheobronchial lymph nodes, died four days after the recognition of an acute myocardial infarction of the anterior wall. Admission to the hospital, nineteen hours before death, was preceded by a sudden attack of pulmonary edema complicated by shock.

An electrocardiogram on admission showed a left bundle branch block pattern with notching of the downstroke of the QRS complex in lead V_3 and progressive lowering of the R wave between leads V_1 and V_3. Eight hours before death the electrocardiogram showed a spreading of the QRS from 0.14 second to 0.26 second, a rate of 109, ventricular extrasystoles, ectopic beats and periods of sinus arrest. Blood pressure at this time was 98/80 mm. Hg, subsequently becoming unobtainable. Just before death, the electrocardiogram showed a bradycardia with complete A-V block and changing ventricular foci, followed by a ventricular tachycardia with rates between 70 and 80, all within a three-minute period. In the final three minutes before standstill, a ventricular flutter lasted for about forty seconds before giving way to ventricular fibrillation.

Blows to the chest, applied after one and a half minutes of fibrillation, failed to elicit the regular beats as noted in the previous patient. After two and a half minutes of fibrillation, standstill occurred, during which blows, although evoking single complexes of extremely low voltage, failed to arouse automatism.

Comment: The lack of response in this patient probably relates to the multiplicity and severity of the pathologic changes. Autopsy revealed, in addition to the acute infarction, focal areas of fibrosis, marked narrowing of the coronary vessels and calcification of the mitral ring.

CASE 11. M. T., aged seventy-one, a farmer who retired ten years ago with symptoms relating to chronic cholecystitis, chronic obstructive pulmonary emphysema and coronary sclerosis with mild hypertension, died fourteen hours after the onset of an acute myocardial infarction. Three years previously an electrocardiogram which, at rest, suggested left ventricular hypertrophy exhibited, after exercise, changes in the RS-T segment consistent with impaired coronary perfusion. At the onset of his attack, an electrocardiogram showed not only an acute infarction of the anterior wall with S-T segment elevations compatible with a pericarditis but also a pattern of an old infarction of the inferior wall.

Terminally, the electrocardiogram recorded a ventricular standstill. After six blows to the precordium a series of 26 automatic beats occurred. During the ensuing standstill several more blows

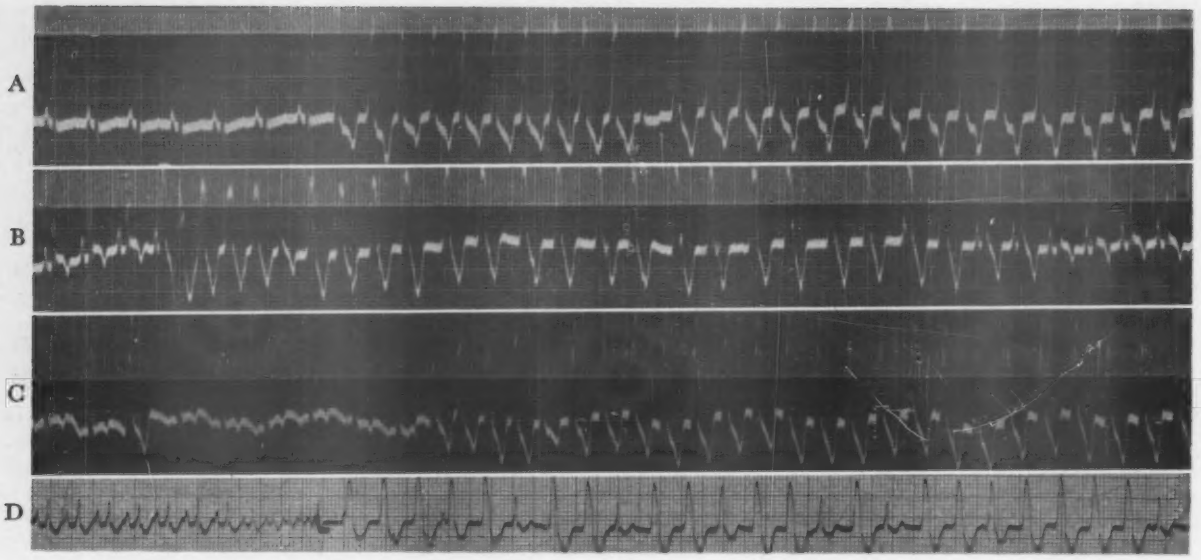


FIG. 9. Four tracings obtained from dogs anesthetized with morphine and nembutal. The tracings are registered in lead II. The heart was exposed. A, a ventricular tachycardia appeared after a solution of sodium oxalate was applied to a small area of the surface of the right ventricle and this area was hit once with a blunt instrument. B, application of sodium citrate at the same area and again hitting once the area of application led to a similar tachycardia. C, in a third dog a 20 per cent solution of sodium chloride was injected subepicardially at the outflow area of the right ventricle; single ventricular extrasystoles appeared (beginning of C); however mechanical stimulation caused a regular tachycardia to appear. D, a regular sinus tachycardia before and coupled ventricular extrasystoles after injection of 0.05 cc. of a 3 per cent solution of sodium oxalate subepicardially on the right ventricle.

finally elicited a series of 61 ectopic beats. Standstill followed during which twenty-two blows delivered over a thirty second-period reawakened an ectopic center.

EXPERIMENTAL OBSERVATIONS

In our case reports we have repeatedly demonstrated that single blows over the heart may result in the formation of a chain of ectopic beats. In each instance the myocardium had been altered by disease leading to varying degrees of hypoxia. Drugs, too, may have exerted their effect. We have implied that the difference in response may depend on the degree of the biochemical and biophysical changes induced by the hypoxia. The greater the deterioration, the less sustained the response.

Experimentally, several agents may be employed to facilitate the production of a multiple response in the mammalian heart following the application of a single induction shock or mechanical stimulus. The animal treated with barium, quinidine and particularly aconitine[7,9] manifests this effect. The intravenous injection of subliminal doses of aconitine alone fails to induce arrhythmias or electrocardiographic changes. One slight stroke with a blunt instrument, such as the handle or back of a knife or handle of a scissors, against the exposed surface of the heart of a treated animal may lead to a long chain of ectopic beats.[8]

Other substances which we have utilized include sodium oxalate, sodium citrate and 20 per cent sodium chloride applied topically. Figure 9A shows the results of a single stroke applied to an area of the heart where 0.05 cc. of an isotonic solution of sodium oxalate was injected into the subepicardium. The single ectopic beat following the stroke is succeeded by a long chain of ectopic beats interrupted only once by a sinus beat breaking through into the ventricle. In another experiment an isotonic solution of sodium citrate injected in the same way provoked a similar response (Fig. 9B). A 20 per cent solution of sodium chloride similarly injected resulted in a chain of 64 ectopic beats appearing when the area of injection was mechanically stimulated (Fig. 9C).

In all these experiments, the ectopic rate, at first rapid, gradually slows until it is overtaken and replaced by the sinus rhythm. If, at this point, cooling of the sinus node slows the sinus rhythm, the ectopic rhythm reappears but soon vanishes. Another feature of the arrhythmias produced under these experimental conditions is the tendency to form grouped beats as shown in Figure 9B.

These chemical agents facilitate impulse formation in form of an after-discharge following mechanical stimulation. This suggests that we may be dealing with oscillatory after-potentials. We know from studies in neurophysiology that the application of citrate or oxalate to a portion of a nerve causing calcium depletion favors the production of oscillations which on reaching a certain threshold value, form propagated impulses. Figure 9D shows that the myocardium responds in a similar way. When 0.05 cc. of a solution of 3 per cent sodium oxalate is injected subepicardially on the right ventricle, normal sinus beats are followed by extrasystoles with fixed coupling.

Comments

These case reports and experimental observations give support to the proposition that mechanical stimulation of the heart offers an immediate, simple and effective method of cardiac resuscitation during standstill. While other methods are being prepared blows to the precordium combined, when indicated, with mouth-to-mouth breathing may successfully maintain life. In our first three cases life appears to have been significantly prolonged by the simple expediency of thumping.

To our knowledge it was during a Morgagni-Stokes-Adams attack in a sixty year old woman that Schott[10] first described the reapperance of the pulse following a blow to the chest. Although this method has received wide attention since Schott's recommendation, many textbooks either do not mention this procedure or discourage the reader by stating that it will be rarely successful. In fact Hosler[4] in his manual on cardiac resuscitation admonishes under the heading *Things Not To Do:* "Do not strike the chest repeatedly."

Blows to the chest wall over the heart have not only prolonged life in our observations, but have also repeatedly reawakened automatism in the ventricular muscle of patients succumbing to intrinsic or extracardiac disease. All these patients had some degree of coronary artery disease, five had acute myocardial infarctions; two had complicating pericardial involvement, tamponade and pericardial adhesions, respectively; two died from extracardiac causes, one with pulmonary embolus and the other with respiratory decompensation. In these cases as deterioration of the heart muscle progressed, periods of cardiac or only ventricular standstill became more frequent. During standstill the response to mechanical stimulation varied with the degree of deterioration within the cardiac muscle. At first a single ectopic beat appeared with each blow. With progressive hypoxia, a chain of ectopic beats would appear with the ventricular complexes becoming wider and developing into ventricular flutter or fibrillation. Subsequently the response was less and less. Complexes of low voltage, with evidence of injury currents, appeared terminally as coupled or single beats. Chains of ectopic beats were more prolonged in two patients (cases 5 and 6) without cardiac disease. In two others (cases 6 and 9) ventricular fibrillation followed thumping and in the former coordinated action from a blow during fibrillation could be established. This could not be duplicated.

A conceivable objection to this method of resuscitation is that, as in cases 6 and 9, a single blow or its resulting tachycardia may lead to ventricular fibrillation. Any impulse reaching the heart during the vulnerable phase may have this effect. However, in our opinion, the implications of standstill are of such gravity that the risk of fibrillation must be taken. As a calculated risk the method, if employed early, affords a better chance of avoiding this complication. The earlier the blows are applied, the better the condition of the myocardium and the more normal the response, that is to say, the more likely a single blow will elicit a single ectopic beat. It is this response that is obtained when the exposed heart is stimulated mechanically[3] or a blow is directed over the precordium of a normal subject.

Even Kipling has not overlooked the medical consequences of a blow to the chest. In *The Drums of the Fore and Aft* the bold, bad drummer boys, Jakin and Lew, consider their prospects of accompanying their regiment into action.

> "Are you medical fit, Piggy?" said Jakin, digging Lew in the ribs with force.
>
> "Yus," said Lew with an oath. "The Doctor says your 'eart's weak through smoking on an empty stummick. Throw a chest an I'll try yer."
>
> Jakin threw out his chest, which Lew smote with all his might. Jakin turned very pale, gasped, crowed, screwed up his eyes and said—"That's all right."
>
> "You'll do," said Lew. "I've 'eard o' men dying when you 'it 'em fair on the breastbone."

Although military organizations have obviously evinced little interest in Lew's test our

curiosity in mechanical stimulation compels us to wish, if somewhat whimsically, that Jakin had been rigged with electrodes when smote.

Experimentally, a single mechanical or electrical stimulus may reawaken spontaneous impulse formation during ventricular standstill. In a damaged heart rapid ectopic impulses may depress an existing spontaneous automaticity. The observations in the present study not only confirm a similar response to mechanical stimuli in the human heart but also redirect attention to a simple measure for the prompt management of ventricular standstill.

Summary

The effects of mechanical stimulation of the heart by blows "fair on the breastbone" are demonstrated in eleven patients. This method is recommended as a routine measure to re-establish automaticity or to maintain cardiac activity while mouth-to-mouth breathing is employed and other methods, such as electrical stimulation or the use of certain pressor amines, are made ready. Blows to the precordium should be tried even if ventricular fibrillation is suspected. Not only may ventricular fibrillation be confused with multiple variform ventricular extrasystoles in the electrocardiogram but it may also be followed by standstill.

The method succeeds in preserving life by evoking ectopic beats which may reawaken cardiac automatism. In the normal heart mechanical stimulation elicits a single response. In the altered, damaged or hypoxic myocardium a blow may produce a multiple response manifested by a tachycardia or even fibrillation.

Experimentally, a prolonged ectopic tachycardia follows mechanical stimulation under the influence of a variety of substances but particularly in the presence of calcium deprivation. This effect is best explained by the formation of oscillatory after-potentials occurring in the wake of a single depolarization.

References

1. Achor, R. W. P. and Edwards, J. E. The fate of patients surviving acute myocardial infarction. *Arch. Int. Med.*, 98: 162, 1956.
2. Cushny, A. R. Stimulation of the isolated ventricle, with special reference to the development of spontaneous rhythm. *Heart*, 3: 257, 1912.
3. Hoffman, A. Die Elektrokardiographie als Untersuchungsmethode des Herzens. Wiesbaden, 1914. Bergman.
4. Hosler, R. M. Manual on Cardiac Resuscitation. Springfield, 1958. Charles C Thomas.
5. Kipling, R. Under the Deodars, The Phantom Rickshaw, Wee Willie Winkie: The Drums of the Fore and Aft, pp. 303, 304. New York, 1899. Doubleday Co.
6. Pruitt, R. D. Cardiac arrhythmia and cardiac death. *M. Clin. North America*, 42: 881, 1958.
7. Scherf, D. Weitere Untersuchungen ueber die Entstehungsweise der Extrasystolen. *Ztschr. ges. exper. Med.*, 58: 221, 1927.
8. Scherf, D. Ueber den Zusammenhang Zwischen festgekuppelten Extrasystolen und extrasystolischen Tachydardien. *Ztschr. ges. exper. Med.*, 70: 375, 1930.
9. Scherf, D., Blumenfeld, S., Golbey, M., Ladopoulos, C. and Roth, F. Experimental ectopic cardiac rhythms. *Am. Heart J.*, 48: 573, 1954.
10. Schott, E. Ueber Ventrikelstillstand (Adams-Stokes'sche Anfaelle) nebst Bemerkungen ueber andersartige Arhythmien passagerer Natur. *Deutsches Arch. klin. Med.*, 131: 211, 1920.

Incidence of Myocardial Infarction Correlated with Venous and Pulmonary Thrombosis and Embolism*

A Geographic Study Based on Autopsies in Uganda, East Africa and St. Louis, U. S. A.

WILBUR A. THOMAS, M.D.†, JACK N. P. DAVIES, M.D. (Bristol), M.R.C.S., L.R.C.P., ROBERT M. O'NEAL, M.D. *and* AMADOR A. DIMAKULANGAN, M.D.

St. Louis, Missouri

REPORTS from East Africa[1] indicate that coronary thrombi and myocardial infarcts are practically non-existent among native Africans who come to autopsy. In contrast, autopsy reports in the United States of America indicate a high incidence of coronary thrombi and infarcts among whites and an intermediate incidence among Negroes.[2–4]

Differences in incidences of coronary thrombi and myocardial infarcts between North Americans and East Africans could be due to differences in degrees of atherosclerosis (local factor) or to differences in the clotting properties of the blood (hematologic factor) or both. It occurred to us that information regarding clotting (unrelated to atherosclerosis) might be obtained by comparing the incidences of thrombotic and thromboembolic phenomena in systemic veins and pulmonary arteries in groups with differing incidences of myocardial infarcts. Thus, if the incidence of pulmonary and venous thrombi was low among Uganda natives (with a low incidence of coronary thrombi and myocardial infarcts) and high among properly matched groups of Americans (with high incidences of coronary thrombi and myocardial infarcts) it would at least suggest that some alteration of a hematologic factor (procoagulative and/or antifibrinolytic) was involved in coronary thrombosis in addition to the local factor of atherosclerosis.

In order to collect information that was as nearly comparable as we could obtain and to compare autopsy procedures and methods of recording autopsy data with those of Washington University, Dr. Thomas visited Makerere College in Uganda, East Africa. After obtaining data from Africa, we obtained comparable data from white and Negro groups of autopsy patients at Washington University in St. Louis of the same age and sex distribution and for the same period.

Our study had two purposes. One was to attempt to confirm, in a direct way, the reports that the incidence of myocardial infarcts was less among autopsied East Africans than among autopsied white or Negro St. Louisans. The other was to determine the degree of correlation between the incidences of myocardial infarcts (which in our experience are usually due to coronary thrombosis) and incidences of thrombotic and thromboembolic phenomena in lungs and veins in the various groups.

MATERIALS AND METHODS

Autopsy reports of patients over forty years of age

* From the Departments of Pathology, Washington University School of Medicine, St. Louis, and Makerere College, University College of East Africa, Kampala, Uganda.

This study was supported in part by Grant H-1820 from the National Heart Institute, Institutes of Health, Bethesda, Maryland.

† Dr. Thomas was a Fullbright Exchange Professor in Baghdad University during the period of this study. Present address: Department of Pathology, Albany Medical College, Albany, New York.

TABLE I

Age and Sex Distribution of Autopsy Patients over Forty Years of Age at Washington University in St. Louis and at Makerere College in Uganda, East Africa, 1951–1956

Age (yr.)	W.U. Whites*		W.U. Negroes		M.C. Negroes*	
	Male	Female	Male	Female	Male	Female
40–49	178	133	33	38	377	62
50–59	335	199	56	26	199	31
60–69	350	223	35	31	98	17
70–79	231	169	23	11	24	5
80+	102	60	3	1	9	5
Total	1,196	784	150	107	707	120

* In this and in following tables W.U. refers to Washington University (Barnes Hospital) and M.C. refers to Makerere College (Mulago Hospital).

TABLE II

Incidence of Thrombi and Thromboembolic Phenomena Among Autopsy Patients over Forty Years of Age at Washington University, St. Louis and Makerere College, Uganda: 632 W.U. Whites Matched by Age and Sex with 632 M.C. Negroes

Data	Male					Female						
Age (yr.)	40–49	50–59	60–69	70–79	80+	40–49	50–59	60–69	70–79	80+	Total	Per Cent Incidence
No. of Autopsies	178	199	98	24	9	68	31	17	6	2	632	
W.U. Whites												
Any Site*	76	110	67	17	5	21	18	10	1	1	326	52
AMI	14	22	9	3	1	2	6	2	1	0	60	9.5
All MI	31	51	32	8	2	2	6	3	1	0	136	22
Lungs and Veins	35	40	24	6	2	13	9	5	0	1	135	21
M.C. Negroes												
Any Site	3	6	4	0	0	0	0	2	0	0	15	2.4
AMI	0	0	0	0	0	0	0	0	0	0	0	0
All MI	0	1	0	0	0	0	0	0	0	0	1	0.16
Lungs and Veins	3	6	4	0	0	0	0	2	0	0	15	2.4

* In this and in following tables "Any Site" refers to the number of patients with any evidence of thrombotic or thromboembolic disease; "AMI" to those with an acute myocardial infarct judged to be less than one month old; "All MI" to those with either acute or healed infarcts or both; "Lungs and Veins" to those patients with thrombi in systemic veins or with pulmonary thromboemboli or pulmonary infarcts.

from Makerere College and Washington University were classified by year, race, sex and age for the period 1951 to 1956. The autopsy series from Uganda consists entirely of Negroes and that from Washington University includes both whites and Negroes but is predominantly white (Table I).

Autopsy reports from the Uganda Negro and Barnes Hospital white population were matched by random pairing of the same sex, age and year. It was possible to match 632 cases from each of the two groups (Table II).

Two hundred and forty-five Uganda Negroes could be similarly matched with an equal number each of Barnes white and Negro population (Table III).

TABLE III

Incidence of Thrombi and Thromboembolic Phenomena Among Autopsy Patients Over Forty Years of Age at Washington University, St. Louis and Makerere College, Uganda: 245 W.U. Negroes Matched by Age and Sex with 245 W.U. Whites and 245 M.C. Negroes

Data	Male					Female						
Age (yr.)	40–49	50–59	60–69	70–79	80+	40–49	50–59	60–69	70–79	80+	Total	Per Cent Incidence
No. of Autopsies	31	61	37	23	3	41	26	17	6	0	245	
W.U. Negroes												
Any Site	7	30	16	16	1	19	11	13	2	0	115	47
AMI	0	6	0	4	0	4	2	3	0	0	19	8
All MI	4	13	3	9	0	8	4	3	1	0	45	18
Lungs and Veins	4	14	9	8	0	9	6	3	2	0	55	22
W.U. Whites												
Any Site	13	34	23	16	1	15	15	11	1	0	129	53
AMI	4	11	10	0	0	0	2	3	1	0	31	13
All MI	6	22	14	8	0	0	4	3	1	0	58	24
Lungs and Veins	7	7	14	6	1	10	9	5	0	0	59	24
M.C. Negroes												
Any Site	0	1	2	0	0	0	0	2	0	0	5	2
AMI	0	0	0	0	0	0	0	0	0	0	0	0
All MI	0	1	0	0	0	0	0	0	0	0	1	0.4
Lungs and Veins	0	1	2	0	0	0	0	2	0	0	5	2

The presence of thrombotic and embolic phenomena in the lungs and veins, heart and other sites was recorded in each of these groups.

In order to characterize further the patients in Uganda, the major diseases found at autopsy were tabulated for 100 consecutive autopsies on individuals over forty years of age for the year 1956. This information is presented in Table IV.

In addition, to link the current study with earlier work, in Figure 1 we give the incidences of acute myocardial infarcts among Negro and white patients at several medical centers in the U. S. A. as reported previously.[2] Only patients over forty years of age are included in Figure 1 so that a better comparison can be made with the results of the present study. It must be noted that (1) only patients with acute myocardial infarcts were included in the previous study, while the present one includes patients with both acute and healed infarcts and (2) the American Negroes in the present study are all from Barnes Hospital, where we previously found a higher incidence of acute myocardial infarction than in any other Negro group.

Results

The results are recorded in detail in Tables I through IV and Figures 1 through 3. The entire autopsy population over forty years of age from Washington University for the period 1951–1956 consisted of 2,237 patients: 1,980 white and 257 Negro. Of the white population 1,196 (60.4 per cent) were males and 785 (39.6 per cent) females; of the Negro population 150 (58.4 per cent) were males and 107 (41.6 per cent) females. There were 827 autopsies on persons over forty years of age in the Uganda group covering the same period: 707 (85.5 per cent) were males and 120 (14.5 per cent) females.

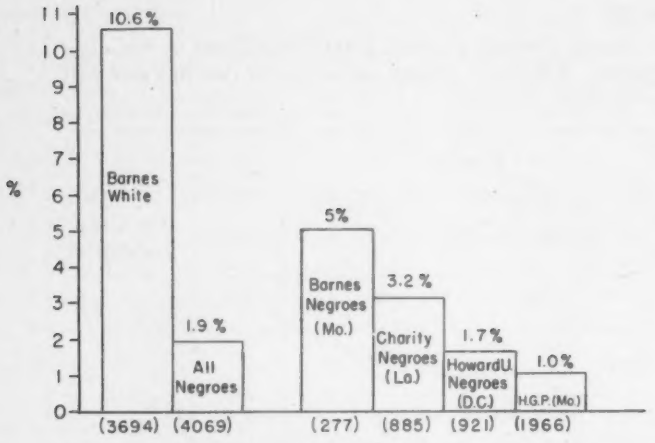


FIG. 1. Comparison of the incidences of acute myocardial infarction among white adults forty to ninety years of age undergoing autopsy at Barnes Hospital, St. Louis and corresponding Negroes undergoing autopsy at St. Louis, New Orleans and Washington, D. C., in the period 1940–1954. These data have been taken from a previous study,[3] and are included for comparison with the current study. It must be emphasized that the data from which this figure was constructed include only those with acute myocardial infarcts while the present study includes those with both acute and healed infarcts. Also, the American Negroes in the current study were all from Barnes Hospital, where the incidence of acute myocardial infarction among Negroes was found to be higher than in other hospitals.

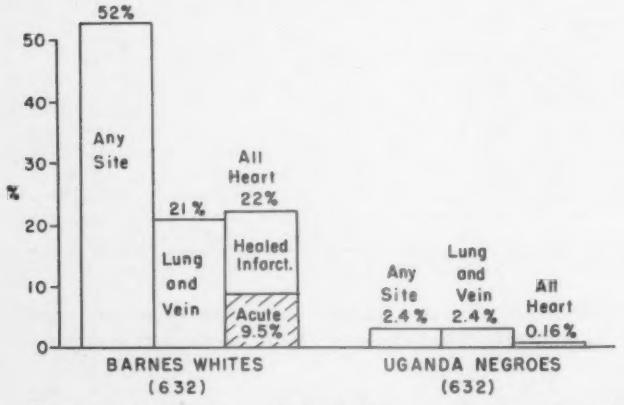


FIG. 2. Comparison of the incidence of thrombi and thromboembolic phenomena among autopsy patients over forty years of age at Washington University, St. Louis and Makerere College, Uganda. Numbers in parentheses refer to the number of patients in each group, matched for age and sex. This figure is derived from the numerical data tabulated in Table II.

In a two-way age and sex matched comparison of 632 cases (Table II and Fig. 2), only one (0.2%) of the Uganda Negroes had a myocardial infarct (MI) and fifteen (2.4 per cent) had pulmonary arterial or systemic venous thrombi or thromboembolic phenomena (VP). Among the American white patients there were 136 (22 per cent) with MI and 135 (22 per cent) with VP. By using the Chi square test, the differences in incidences of either MI or VP between the American white patients and Uganda Negroes were found to be highly significant ($P < 0.001$ for each comparison).

In a three-way age and sex matched comparison of 245 cases (Table III and Fig. 3), one (0.4 per cent) Uganda Negro had MI and five (2 per cent) had VP; forty-five (18 per cent) of the American Negroes had MI and fifty-five (22 per cent) had VP; and fifty-eight (24 per cent) of the American white patients had MI and fifty-nine (24 per cent) had VP. Using the Chi square test, the differences in incidences of either MI or VP between the American white patients and American Negroes were not significant ($P > 0.1$ for each), but between the Uganda natives and either of the other two groups these differences were highly significant ($P < 0.01$ for each comparison).

TABLE IV

List of Major Diseases and Their Frequency in 100 Consecutive Autopsies in Patients over Forty Years of Age Performed at Makerere College in 1956

Disease	Frequency
Trauma	14
Tuberculosis	13
Tertiary syphilis	13
Pneumonia	11
Cancer	11
Portal cirrhosis	8
Lung abscess & bronchiectasis	4
Peptic ulcer	3
Pyelonephritis	3
Meningitis	3
Strangulated hernia	2
Chronic renal disease	3
Amebiasis	2
Acute hepatic necrosis	2
Tetanus	2
Prostatitis	2
Other diseases occurring only once:	
Dysentery	
Volvulus	
Bacterial endocarditis	
Peritonitis	
Liver abscess	
Rheumatic heart disease	
Prostatic hypertrophy	
Polycystic kidney	
Cerebral hemorrhage	
Onchocerciasis	
Endomyocardial fibrosis	
Amyloidosis	
Acute alcoholism	
Pulmonary embolism	

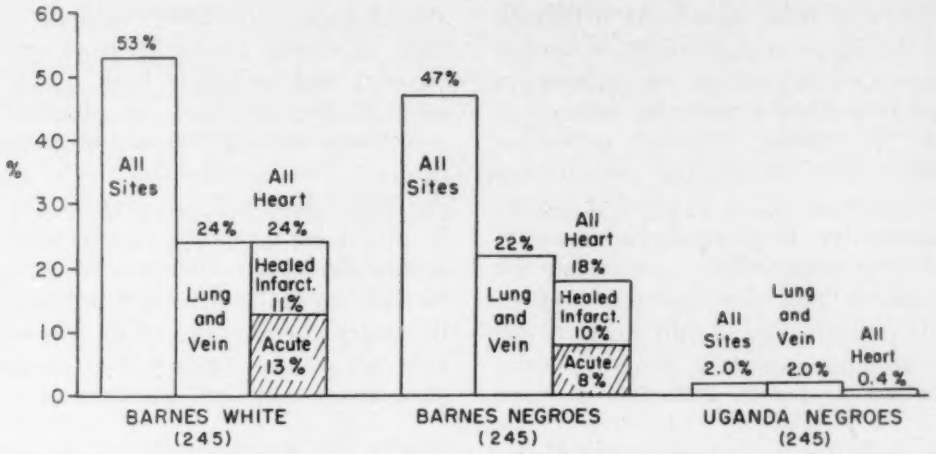


FIG. 3. Comparison of the incidence of thrombi and thromboembolic phenomena among white and Negro patients over forty years of age undergoing autopsy at Washington University, St. Louis and Negro patients undergoing autopsy at Makerere College, Uganda. This three-way age and sex-matched comparison is based on the numerical data in Table III. Note the similarity between the incidence of thrombi in lungs and veins and the incidence of myocardial infarcts in each of the three groups of autopsy patients.

COMMENTS

Dr. Davies, during visits to the U. S. A., and Dr. Thomas, during his visit to Uganda, found autopsy technics in Uganda and the U. S. A. to be similar. In Uganda the autopsies are performed by Dr. Davies and other trained pathologists, while in St. Louis they are performed by a resident-in-training, but all organs in each case, including heart and lungs, are checked by a qualified senior pathologist. It would appear that data derived from autopsies performed at Washington University are reasonably comparable to data derived from autopsies in Uganda. Thus it seems fair to conclude that this study provides direct confirmation of the reports[1,2] that myocardial infarcts are more commonly found in either white or Negro patients undergoing autopsy at Barnes Hospital in St. Louis than in Negroes undergoing autopsy at Makerere Medical College in Uganda. Differences in age and sex composition of the autopsy populations could not account for the difference in incidences of myocardial infarcts, because in this study all the groups were matched for age and sex. A similar conclusion can be drawn regarding the incidences of thrombotic and thromboembolic phenomena in lungs and veins in autopsy patients.

It is not known how closely the autopsy populations reflect the general populations in the two areas. However, evidence from all sources (clinical observations, vital statistics and autopsies) indicates high incidences of myocardial infarcts and thrombotic and thromboembolic phenomena in lungs and veins of those in the U. S. A. and low incidences in those from Uganda and elsewhere in Africa.[5] Myocardial infarction is almost unheard of clinically among Uganda Negroes; however, physicians are quite familiar with the disease because of the high incidence among immigrants to Uganda from India. Similarly, pulmonary embolism is rarely seen clinically among Uganda Negroes, even in the most difficult surgical cases.

Regardless of how closely or remotely the autopsy populations reflect the general populations, we have available for study autopsy groups with high and low incidences of myocardial infarcts. In these groups we found a close correlation between the incidence of myocardial infarction and the incidence of thrombotic and thromboembolic phenomena in lungs and veins. Several possibilities must be considered in attempting to account for this correlation.

It is well known that myocardial infarction itself is frequently complicated by thrombotic phenomena elsewhere, either from mural cardiac thrombi breaking off or from venous thrombosis associated with *congestive failure*. In order to determine whether or not the correlation was due to these associations, we re-evaluated the data eliminating all cases of myocardial infarction. The results were not significantly altered. Other causes of congestive failure, such as rheumatic heart disease and renal hypertension, appear to be about equally common in Uganda and the U. S. A. It seems unlikely that congestive failure is the common denominator.

The *local factor of stasis* associated with lack of activity of the leg muscles (milking action) is important in venous thrombosis and differences in physical activity could account for differences in incidence. In Barnes Hospital in recent years physical activity of hospital patients has been encouraged in an effort to prevent thrombotic complications. In Uganda it is sometimes difficult to prevent activity, even when the physicians consider inactivity desirable. However, it seems unlikely that a difference in this local factor of stasis accounts for the entire difference in incidences of thrombi in these groups.

It appears that the most logical conclusion to draw from the data presented herein is that some common *hematologic factor* (procoagulative and/or antifibrinolytic) is operating on both the venous and coronary arterial systems and that differences in this factor account, at least in part, for the observed differences between the geographic areas in the incidence of all thrombotic phenomena (heart, veins, lungs). Similar conclusions have been reached by Robertson[6] in a study of Jamaicans and Americans, by Morris[7] in a study of old and recent autopsy records in England and by Dedichen et al.[8] in a study of the sudden drop in the incidence of myocardial infarction in certain countries during the war years.

These conclusions do not mean to imply that the *local factor of atherosclerosis* is unimportant in coronary thrombosis. It is likely that the Uganda Negroes had less coronary atherosclerosis than the other groups and that this accounted in part for the virtual absence of infarcts.

If, as we have suggested, a hematologic factor *is* important in coronary thrombosis (in addition to a local factor), it should be possible to reduce the incidence of coronary thrombosis in a population by altering the hematologic factor even in the presence of the same amount of atherosclerosis. However, in order to do this, we need to know what affects the hematologic factor. The current study provides no information on this point. There are too many uncontrolled elements, such as diet,[9] body weight,[10] climate,[11] activity,[12] and the presence of other diseases. Further study will be necessary.

In a previous study (Fig. 1) we observed that acute myocardial infarcts were found at autopsy significantly more often among white patients than among Negroes, even at Washington University. In the present study, limited to Washington University Negroes (where the high incidence among Negroes was noted previously) and including both healed and acute infarcts, the incidence of myocardial infarcts was lower among Negroes than among white subjects, but in these relatively small samples the difference was not statistically significant. It might be tempting to conclude from these figures that the incidence of myocardial infarcts in Negroes has increased to approximately that of whites since the last study was made. However we do not believe that we have enough data to warrant such a conclusion.

Summary

Recent autopsy records at Washington University in St. Louis and Makerere College in Uganda, East Africa were reviewed to determine the incidences of venous thrombi and pulmonary thromboembolic phenomena, as well as the incidences of myocardial infarcts, in three groups of patients: (1) St. Louis white patients, (2) St. Louis Negroes, and (3) Uganda Negroes.

The incidence of myocardial infarcts was high in St. Louis white patients, intermediate in St. Louis Negroes and practically nil in Uganda Negroes; the only infarct found in Uganda among 1,427 patients over forty years of age was a small healed one.

The incidence of venous thrombi and pulmonary thromboembolic phenomena closely paralleled the incidence of myocardial infarcts in the three groups.

The studies reported herein suggest that differences in the general tendency of the blood to clot and/or lyse account, at least in part, for the differences in the incidences of coronary thrombosis and myocardial infarction that exist between autopsied Ugandans and St. Louisans. Further investigation must be carried out utilizing many technics before the suggestion can be established as fact. Other studies will then be necessary to determine the precise nature of the difference and the reason for it, i.e., dietary, emotional or genetic.

Probable, but as yet unestablished, differences in the degree of atherosclerosis present in the three groups may also contribute to the differences in incidences of myocardial infarction, but since the local factor of atherosclerosis is not present in veins, it could not account for the observed differences in evidences of venous thrombosis.

References

1. Davies, J. N. P. Kwashiorkor. In: Liver Injury, p. 151. Edited by Hoffbauer, F. W. New York, 1950. Josiah Macy, Jr. Foundation.
2. Thomas, W. A., Blache, J. O. and Lee, K. T. Race and the incidence of acute myocardial infarction. *Arch. Int. Med.*, 100: 423, 1957.
3. Keil, P. G. and McVay, L. V. A comparative study of myocardial infarction in the White and Negro races. *Circulation*, 13: 712, 1956.
4. McVay, L. V. and Keil, P. G. Myocardial infarction with special reference to the Negro. *Arch. Int. Med.*, 96: 762, 1955.
5. Letac, R., Mawupe Vovor, V. and Cabanne, F. De la rarete de la pathologie veineuse des membres inferieurs en Afrique Noire. *Schweiz. Ztschr. allg. Path.*, 21: 587, 1958.
6. Robertson, W. B. Atherosclerosis and ischemic heart-disease: observations in Jamaica. *Lancet*, 1: 444, 1959.
7. Morris, J. N. Recent history of coronary disease. *Lancet*, 1: 1, 1951.
8. Dedichen, J., Strom, A., Adelsten-Jensen, R. and Closs, K. Incidence of atherosclerotic disease during war years. In: Factors Regulating Blood Pressure, p. 117. Edited by Zweifach, B. W. and Shorr, E. New York, 1951. Josiah Macy, Jr. Foundation.
9. Stare, F. J.: Editorial. Nutrition, atherosclerosis, and infarction. *Am. J. Clin. Nutrition*, 7: 3, 1959.
10. Keys, A. Relative obesity and its health significance. *Diabetes*, 4: 447, 1955.
11. Heyer, H. E., Tend, H. C. and Barris, W. The increased frequency of acute myocardial infarction during summer months in a warm climate: a study of 1,386 cases from Dallas, Texas. *Am. Heart J.*, 45: 741, 1953.
12. Morris, J. N. and Crawford, M. D. Coronary heart disease and physical activity of work. *Brit. M. J.*, 2: 5111, 1958.

Coronary Heart Disease in the South African Bantu*

W. Laurie, D.S.O., M.D., T.D.D.,† J. D. Woods, M.B., F.R.F.P.S., M.R.C.P.‡ *and* G. Roach, M.B., CH.B.‡
Natal, South Africa

In this study, the term "coronary heart disease" includes "the various effects of coronary arterial disease on the heart, deleterious enough to cause symptoms or signs or post-mortem evidence of more than trivial damage to the heart. Thus a myocardial ischaemia with angina pectoris, or ECG abnormalities due to coronary disease, acute myocardial infarction and old scars, are all included under this heading."[32] It is misleading to use the term "coronary artery disease" synonymously with "coronary heart disease" as is done by some workers.[26]

Much attention has been paid to the claim that coronary heart disease is rare in the South African Bantu[6,11,15,29] but comparison of population incidences of diseases may be misleading. Mann[21] describes such comparisons as unprofitable, and Reid[25] considers comparisons between British and Bantu to be treacherous and quite unrealistic. Higginson and Pepler[16] point out that "no vital statistics are available for the Bantu of South Africa, and knowledge of their disease patterns is dependent on clinical impressions and on examinations of hospital material which is of necessity selected; this involves numerous fallacies."

The danger of relying on unsupported clinical diagnosis in coronary heart disease is well brought out by Paton[23] who reviewed autopsy findings on patients in Edinburgh thought to have died of myocardial infarction. When electrocardiograms had not been taken, he found an accuracy rate of only 44 per cent; this low rate was due both to overdiagnosis and to underdiagnosis. He pointed out that electrocardiographic diagnosis of recent myocardial infarction is accurate and that an unsupported clinical diagnosis is no longer justifiable. Hunter[18] showed that when the possibility of myocardial infarction is not readily brought to mind, as with Negro patients, the accuracy of unsupported clinical diagnosis sinks to nil.

To date, little has been reported of adequate clinical investigation into heart disease in the South African Bantu. There are only two relevant postmortem studies[1,16] which do not support the theory that coronary artery disease and coronary heart disease are rare in the Bantu. While Higginson and Pepler[16] think that severe coronary artery disease is less frequent in the hospitalized Bantu of South Africa than in hospitalized Americans and Danes, they did not find the differences to be wholly conclusive. Becker,[1] in his series of 3,000 autopsies (of which 70 per cent were drawn from Bantus), particularly studied 247 patients with hypertensive heart disease and noted "the coronary vessels are frequently diseased in this condition and the myocardium is frequently damaged." In these 247 patients everyone over the age of forty years had coronary atherosclerosis. Becker's findings do not necessarily give the true incidence of coronary heart disease in the Bantu. He points out that "no true reflection of the number of persons dying from acute cardiac failure can be given in these statistics as such cases are diverted through a legal formality to the medico-legal authorities."

From these reports it appears that coronary atherosclerosis occurs in the Bantu more commonly than is generally supposed. There is one other important reason for questioning the accuracy of clinical impressions of the incidence of heart disease in the Bantu. Neither Becker[1] nor Higginson and Pepler[16] in their series reported any large incidence of deaths from heart failure of unknown etiology in Bantus, but such a grouping is found in clinical reports from the

* From Edendale Hospital and Provincial Pathology Service, Natal, South Africa.
† Present address: Public Health Laboratory Service, Perth, Western Australia.
‡ Present address: Department of Cardiology, University of Alberta Hospital, Edmonton, Canada.

same school. Schwartz et al.[29] classify no less than 37.5 per cent of their Bantu patients with cardiac disease as suffering from heart disease of unknown etiology; these authors do not accept the view of Higginson et al.[15] that the cause is probably nutritional.

In view of these discrepancies we undertook a clinicopathologic study into the problems of coronary heart disease in the South African Bantu. The clinical study extended over six consecutive months, and the pathology investigation extended over a twelve-month period.

Material

This study is based on findings at Edendale Hospital which serves a local population of almost 100,000 non-Europeans in this area and a very much greater number in the outlying areas. With the exception of a very small number of Asiatic patients, ignored in this study, our hospital population is Zulu, a pure Bantu race. Only 15 per cent of the patients are drawn from the urban area of Pietermaritzburg; the remaining 85 per cent come from the native reserves where they live in a fashion typical of the great mass of the Bantu of Africa. Such a mode of living is in striking contradistinction to the mode of life of the urban, detribalised, mixed communities which make up the population of the great cities of South Africa, and which provided the material for the clinical and pathological studies previously reported. Other important factors may have influenced our results. First, this is the only large non-European hospital in the area and there is no selection in the admission of patients. Second, there is no selection in the carrying out of autopsy examinations other than the wishes of the patients' relatives; even persons dying suddenly are autopsied by us and not by the medicolegal authorities unless unnatural death is suspected. In the year under review about 75 per cent of all patients who died in this hospital came to autopsy. Last, as we are dealing with a static population, readmissions are common and follow-up studies are possible.

Clinical Study

All patients admitted to the adult medical wards of Edendale Hospital with cardiac symptoms as their main complaints were studied over a period of six consecutive months covering both hot and cold weather. Patients in whom symptomless cardiac disease was found were not included, with the exception of three patients admitted for mitral valvotomy. The series thus consisted almost exclusively of patients in cardiac failure. Routine investigations included a careful history-taking, physical examination, x-ray examination of the chest, blood Wassermann reaction, electrocardiogram, blood count and urinalysis; when necessary, such tests were repeated and other tests made.

In the event of death every effort was made to confirm the diagnosis by autopsy; of the patients who died in this series, 77 per cent came to autopsy examination. In these cases special notice was taken of the state of the heart and the coronary arteries. In four additional instances the diagnosis was confirmed at operation. Autopsy or operative proof of the diagnosis was obtained in over 23 per cent of all the cardiac patients admitted to the series.

Table I lists the types of heart disease encountered. Eighteen of the fifty-eight deaths occurred within forty-eight hours of admission. Therefore it was not always possible to complete the investigations. Thirty-seven patients were admitted on more than one occasion during the period of study. This gives a total of 206 patients with 243 cardiac admissions, which is approximately 21 per cent of all medical admissions to this hospital for persons over ten years of age.

From previous case records it was found that 10 per cent of the hypertensive group in the series were examples of decompensated hypertension, i.e., patients admitted in cardiac failure with blood pressures within normal limits, but with records of previous admissions for hypertensive cardiac failure. In our experience this finding is common in the Bantu although not limited to this race. In the white races, however, when decompensation occurs in the absence of myocardial infarction, the fall in blood pressure usually affects the systolic pressure more than the diastolic, with the latter usually remaining somewhat elevated and indicating the underlying pathology.[8] In the Bantu both pressures commonly fall to well within the accepted limits of normal, and in the absence of previous clinical records the diagnosis of hypertensive disease may be difficult to establish. In such cases the electrocardiogram is of considerable value as the pattern of left ventricular hypertrophy usually persists.

From this series we have found significant differences in the incidences of cardiac diseases both compared with the findings of Becker[1] in his autopsy series and with the clinical series reported by Schwartz et al.[29] (Table II).

These percentages are not strictly comparable. In Becker's series all patients were in cardiac failure and

TABLE I

Age and Sex Distribution and Nature of Cardiac Disease in Patients Admitted in Six-Month Period to Medical Ward

Age (yr.) and Sex		Rheumatic	Pulmonary	Pericarditis	Hypertensive	Miscellaneous	Syphilitic	Unknown	Total
5–14	M...	1	0	0	0	0	0	0	1
	F....	2	0	0	0	1	0	1	4
15–24	M...	2	0	0	0	0	0	3	5
	F....	4	0	2	1	0	0	1	8
25–34	M...	4	0	0	2	2	1	1	10
	F....	9	1	4	1	1	1	2	19
35–44	M...	3	1	2	10	0	2	9	27
	F....	9	2	2	5	1	0	4	23
45–54	M...	2	2	1	6	0	4	6	21
	F....	1	2	0	7	1	4	5	20
55–64	M...	1	3	0	5	0	2	8	19
	F....	1	0	0	3	0	3	6	13
65+	M...	0	2	0	5	0	2	11	20
	F....	0	1	1	5	0	1	8	16
Total.....		39	14	12	50	6	20	65	206
Deaths.....		4	2	7	17	0	4	24	58
Autopsies.....		3	1	5	12	0	3	21	45
Operation....		3	0	1	0	0	0	0	4

the diagnosis was made at autopsy. In the series of Schwartz et al. the figures are for all cases of heart disease admitted, not necessarily in failure, and the diagnosis was made on clinical and autopsy evidence. In our series all but three patients were in cardiac failure and the clinical diagnosis only is given.

The incidence of myocardial infarction given by Schwartz et al. was 0.36 per cent. In Becker's series myocardial infarction was not found as a cause of cardiac failure although he describes six cases of myocardial infarction in the larger series of 3,000 autopsies. In our series no case of myocardial infarction was definitely diagnosed clinically.

The findings in the two clinical studies, Schwartz et al.[29] and ours, are much the same except for the incidence of syphilitic heart disease in which our figures are much higher than those of Schwartz et al. and approach those of Becker.

There is a striking difference between Becker's autopsy series and the two clinical series concerning the incidence of unknown heart disease. In the autopsy series there is virtually no group of cardiac deaths from disease of unknown etiology whereas this forms the largest group in both clinical studies. This finding is of much importance.

In view of the numerical importance of the "unknown" group of cardiac deaths it was decided to examine this problem while investigat-

ing the incidence of coronary heart disease in the South African Bantu.

Cases With Evidence of Myocardial Ischemia

In a study of coronary heart disease, three distinct features must be considered, namely, myocardial infarction, angina pectoris and cardiac failure due to ischemic degeneration of the myocardium.

MYOCARDIAL INFARCTION

Of six patients originally classified as "unknown," three had myocardial infarction proved at autopsy and three were considered to have possible myocardial infarction on clinical grounds.

Case 1. A twenty-two year old man was admitted in acute cardiac failure with a vague history of chest pain. The electrocardiogram showed a left bundle branch block without significant Q waves or ST segment changes. He died soon after admission.

At autopsy a large anterior infarct was found associated with thickening of the coronary arteries but with no thrombus in any of the major vessels.

Case 2. A forty year old man was admitted with acute cardiac failure but no history of precordial pain. The electrocardiogram showed progressive changes culminating in a pattern of diminishing R waves across the precordium to a point between V_4 and V_5 where a small localized Q wave was found. This was followed in V_5 by an RS pattern. After a stormy illness he recovered, but was admitted dying two months later.

Autopsy showed a healed posterior infarct of the epicardial surface of the left ventricle and several large areas of fibrosis in the anterior wall. Plaques of calcified atheroma were found in the left coronary artery, but no occlusion could be demonstrated.

Case 3. A fifty-eight year old woman was admitted in severe congestive failure with a vague history of precordial pain. She died before an electrocardiogram could be taken.

At autopsy a larged healed infarct of the left ventricle was found. Both coronary ostia were narrowed by syphilitic aortitis, but no atheroma or occlusion could be demonstrated.

Case 4. A sixty-five year old woman was admitted in severe congestive failure following an attack of epigastric pain which radiated through to the back. The electrocardiogram showed changes suggestive of an anteroseptal infarct. She died six hours after admission and autopsy was refused.

Case 5. In a forty-eight year old man, a sudden severe precordial pain developed, lasting three hours. He was admitted to the hospital the next day. Serial electrocardiograms showed changes suggestive of damage to the epicardial surface of the left ventricle, but at no time did he show clinical or radiological signs of pericarditis.

TABLE II
Comparisons of Incidence of Cardiac Disease as Reported by Three Groups

Type of Disease	Incidence of Disease (%)		
	Becker[1]	Schwartz et al.[39]	Present series
Rheumatic	23.5	23.6	18.9
Pulmonary	10	10.9	6.8
Hypertensive	28.6	19.6	24.2
Syphilitic	16.9	1.1	9.7
Pericarditis	8	4	5.8
Miscellaneous	9.6	3.2	3
Unknown	4	37.5	31.5

Case 6. In a forty year old man under investigation for a renal condition, a severe constricting precordial pain suddenly developed associated with dyspnea and sweating. This pain lasted for four hours and was associated with an elevated blood pressure. The electrocardiogram taken before the onset of this episode was normal, but subsequent to the attack changes suggestive of epicardial damage became evident. No evidence of pericarditis or pericardial effusion was found.

ANGINA PECTORIS

In this study, careful history-taking of the events preceding the onset of congestive failure established that the Bantu, on occasion, complains of symptoms strongly suggestive of angina pectoris. Gelfand[9] found angina pectoris to be not uncommon in Bantus suffering from syphilitic aortic disease, but did not describe angina as a result of coronary heart disease. Schrire and Uys[27] reported angina present in two of the three patients subsequently found at autopsy to have myocardial infarction. In the present study anginal symptoms were found both in patients suffering from syphilitic aortitis and also among those with other types of heart disease.

The possibility of angina pectoris was considered when the patient complained of substernal pain, with or without radiation, brought on only by exertion and relieved rapidly by rest. Less attention was paid to the quality of pain as the descriptive powers of the Bantu are limited. Although histories given by Bantu

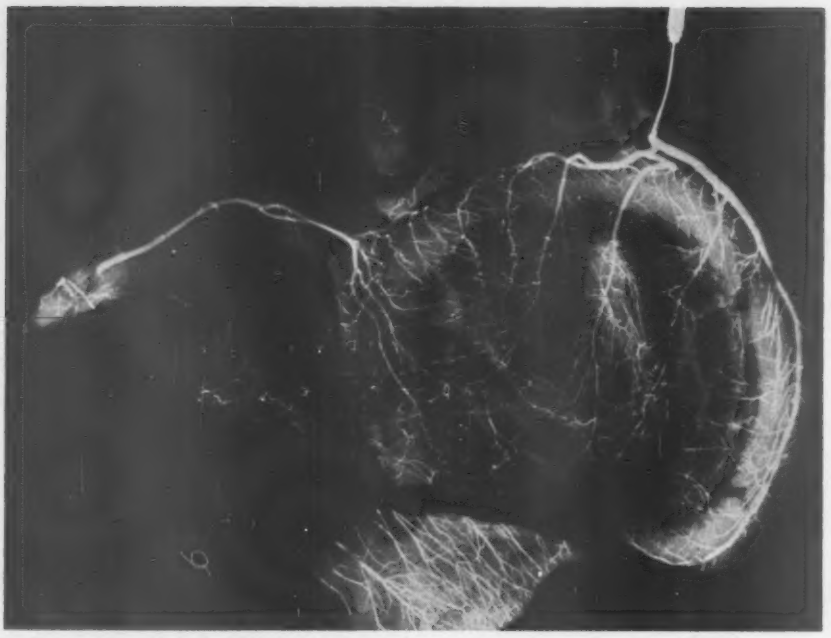


FIG. 1. Syphilitic occlusion of right coronary ostium with anastomotic supply to right side from left.

patients are commonly unreliable, we were impressed by the fact that on the subject of chest pain we usually obtained a very definite history one way or the other.

Autopsy Findings in Patients with Anginal Symptoms: Five patients complaining of angina pectoris died and came to autopsy. The clinical diagnoses were hypertensive heart disease (two), unknown heart disease (two) and syphilitic aortitis (one). The patients with "unknown" heart disease showed autopsy evidence of malignant hypertension and nephrosclerosis, respectively. Moderate atheroma with partial occlusion of the left coronary artery was found in three of the four patients with hypertensive cardiac disease and severe ostial narrowing in the patient with syphilitic cardiac disease.

CASE 7. *Syphilitic aortitis:* This thirty-six year old man gave a history of angina on exertion proceeding to angina decubitus. He was admitted three times in congestive failure. Electrocardiograms showed left ventricular hypertrophy with marked ST segment depression.

At autopsy his heart weighed 24 ounces. The right coronary orifice was obliterated by severe syphilitic aortitis and the left reduced to a diameter of less than 2 mm. Perfusion of this heart through the left coronary artery showed a complete anastomosis with the right coronary artery which ended blindly $^1/_3$ inch from its ostium (Fig. 1). There seemed little doubt that he suffered from true angina.

Angina Pectoris in Surviving or Non-autopsied Patients: These 26 cases consisted of the following: four had hypertensive failure, one malignant hypertension; six had aortic valvular disease thought to be due to syphilis; sixteen had cardiac failure of unknown etiology. Four of these sixteen had renal disease and may have been instances of decompensated hypertension. Four others had serological evidence of syphilis but no signs of aortic disease. The remaining eight, all between sixty and eighty years of age, had no evidence of syphilis or renal disease.

In these twenty-six patients the cardiographic findings were as follows: normal, four cases; left ventricular hypertrophy, ten cases; left ventricular hypertrophy and partial heart block, one case; left bundle branch block, three cases; low voltage QRST complex, three cases; inversion of first four precordial T waves, one case; QS following rS pattern in precordial leads, three cases; diminishing precordial R wave as far as V_4, one case.

In the three instances in which a QS followed an rS pattern in the chest leads, QS occurred in V_3 in two cases and in V_4 in the other. In both cases a qR pattern followed in the next lead.

In the autopsied patients the findings were compatible with myocardial ischemia, and if this is accepted, the pain of which these patients complained was probably true angina pectoris.

TABLE III
Findings in Fourteen Patients with Myocardial Fibrosis

Age (yr.) and Sex	Myocardial Hypertrophy	Coronary Sclerosis	Associated Disease	Electrocardiographic Findings
Hypertensive patients (4):				
36, M.	Left	+++	Malignant hypertension	Left bundle branch block
37, M.	Left	++	...	Inverted T wave in V_{1-4}
40, M.	Left	++	...	Left bundle branch block
61, F.	Left	+	...	Flat T waves
Cardiac failure of unknown etiology (10)				
50, M.	Left and right	+	Nephrosclerosis	Right ventricular hypertrophy and partial heart block
64, M.	Left	0	Mitral stenosis, mitral insufficiency	...
58, M.	Left and right	0	Nephrosclerosis	Right ventricular hypertrophy
48, M.	Left	0	Aortic stenosis	Left ventricular hypertrophy
64, F.	Left	0	Nephrosclerosis	...
48, M.	Left	Narrowed ostia	Aortic stenosis	Left ventricular hypertrophy
55, M.	None	+++	...	Heart block
56, F.	Left	+++	Pyelonephritis	Heart block
65, F.	Left	+++	Nephrosclerosis	...
70, M.	Left	++	...	...

No such evidence can be given in those who survived or did not come to autopsy. Since the symptoms and illnesses from which this latter group suffered resembled closely those of the autopsy group, it would appear that, in some of these patients at least, myocardial ischemia was the cause of the chest pain.

It is noteworthy that in the instances of syphilitic aortitis, where the vexing question of coronary atheroma does not arise, the symptoms and electrocardiographic findings were the same as those found in the non-syphilitic group.

CARDIAC FAILURE DUE TO ISCHEMIC MYOCARDIAL DEGENERATION

Wearn (quoted by Fishberg[8]) has shown that in hypertensive myocardial hypertrophy, although the individual fibers enlarge, there is no corresponding increase of the capillary blood supply. Ischemia thus tends to develop, and Fishberg considers that the fibrosis found in hypertrophied hearts is always ischemic in nature. When decompensation occurs and the coronary filling pressure drops, this ischemia must be intensified owing to the greatly reduced coronary blood flow. Similar fibrotic changes are found when the ischemia is due to atheromatous narrowing of the coronary arteries or their ostia. These degenerative changes may weaken the myocardium to such an extent that cardiac failure may supervene.[24]

Analysis of the relevant findings in persons with myocardial fibrosis found at autopsy is shown in Table III.

The areas of fibrosis in the hearts of the first two hypertensive patients were as large as peas and may well have been healed infarcts. In all fourteen patients, factors known to cause myocardial ischemia were present and it would appear probable that the myocardial fibrosis was ischemic in origin.

Cardiac Failure of Unknown Etiology

This group originally formed 31.5 per cent (sixty-five patients) of the series. Of these, thirty-four have already been considered and the probable diagnosis discussed. Thirty-one patients remain in whom the diagnosis is still to be discussed. Of these, six were autopsied; three of the six died of tuberculous pericarditis, one died of amebic pericarditis and the remaining two from decompensated hypertension.

The clinical features found in the survivors were usually those of failure of both sides of the heart. Cardiac enlargement was invariable and was often so great as to prompt exploratory pericardial tapping even in the absence of other clinical signs of pericardial effusion. In five patients decompensated hypertension was suggested by the finding of appropriate renal changes.

The cardiographic findings were as follows: left ventricular hypertrophy, six cases; bundle branch block, four cases; partial heart block, three cases; flat T waves, six cases; disorders of rhythm, two cases; QS in V_4 after rS in V_3, one case; diminishing R wave as far as V_4, one case.

The findings in all of the twenty-one autopsied patients fit into well recognized disease patterns. Autopsy examinations failed to reveal any evidence of a new cardiac disease peculiar to the Bantu. Decompensated hypertension apparently accounted for the cardiac failure in 24 per cent of this "unknown" group and, when added to the 10 per cent of the hypertensives known to have this condition, is clearly an important factor in the production of cardiac failure of unknown or obscure origin.

Symptoms strongly suggestive of angina pectoris occurred in nearly 30 per cent of this group with cardiac failure of unknown etiology. When autopsy evidence was obtained, these symptoms appeared to be due to ischemia either from decompensated hypertension or coronary atherosclerosis. The symptoms did not differ in any significant manner from those found in patients with syphilitic aortitis in whom the disputed question of coronary atheroma does not arise.

The clinical and electrocardiographic findings of those patients of this group who did not die are similar to those found among the cases coming to autopsy. It would appear reasonable to assume that the same underlying pathology was operating in at least some of the survivors, and that the so-called "cryptogenic" group of cardiac patients consists largely of undiagnosed cases of well recognized causes of heart disease, notably decompensated hypertension, pericardial disease and coronary heart disease.

Pathology Study

The pathology section of this study had three main objects: (1) to investigate the incidence in the South African Bantu of coronary atherosclerosis (coronary artery disease), (2) to investigate the effects of such arterial disease on the myocardium and (3) to investigate the large group of clinically unidentified cases of cardiac disease in the Bantu.

Method: Autopsy examinations numbering 1,048 were carried out by one of the authors. The age grouping of our series differs very markedly from that of Becker.[1] Over 50 per cent of the 1,048 autopsies were on infants under the age of two years. In view of this, an element of selection was allowed to operate at first, whereby a full cardiac investigation was made only on hearts from persons thought to have cardiac disease. After some months this laborious cardiac investigation was extended to include all patients coming to autopsy.

After a full autopsy examination had been completed, each heart was immersed in a heated saline bath and was perfused through one coronary artery, first with saline then with a radiopaque gelatin mass. The heart was next immersed in iced saline to fix the gelatin mass and then was "unrolled" to take a skiagram to show the two sides of the heart separately. Next, each coronary artery was dissected and opened as far as possible; then pieces of heart tissue were taken for microscopic examination. The tissues always included portions of each ventricle and the septum, and any other area thought necessary following serial slicing of the whole heart. A preliminary report on the skiagram findings has been published[20] and will not be discussed further.

The most serious drawback in this work[14] is that no satisfactory generally accepted standards exist. We attempted to allow for this in two ways. First, during the actual work with the heart both of the Edendale authors (W. L. and J. D. W.) independently assessed the findings. Second, all heart tissues for microscopic examinations were submitted to independent Durban workers as routine specimens; these histopathologists were not aware of the nature of our investigations. Such workers included persons from the Natal Service, Government pathologists and the staff of Durban Medical School. At the end of the study a further review of the material was carried out by Dr. Roach of the Natal Service.

Incidence of Coronary Atherosclerosis

This full cardiac investigation was made on 513 patients who came to autopsy during the year of work. The first problem under study concerned the incidence of coronary atherosclerosis in the South African Bantu.

Grading of Atherosclerosis: We attempted a wide classification of the grade of atherosclerosis as suggested by Wigle,[33] but unlike him omitted all reference to x-ray changes since such appearances are misleading in our experience. Our suggested classification is:

Grade 1: Both coronary orifices normal and the coronary arteries free from disease.

Grade 2: Reduction of one coronary artery to not less than three-quarters bore over an aggregate distance of at least $^1/_2$ inch.

Grade 3: Narrowing of one coronary ostium to one-quarter bore or narrowing of one coronary artery to half diameter over an aggregate distance of at least $^1/_2$ inch.

Grade 4: Reduction of both coronary orifices each

TABLE IV

Incidence of Coronary Atherosclerosis in the South African Bantu (Age Groups Thirty-five Years and Over)

Age (yr.) and Sex		Grading of Coronary Atherosclerosis										Total	
		1		2		3		4		5			
		No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
35–44	M...	30	12.3	7	2.8	5	2.0	1	0.4	2	0.8	45	18.5
	F....	20	8.2	3	1.2	1	0.4	..	..	..	..	24	9.9
45–54	M...	28	11.6	11	4.5	9	3.7	5	2.0	1	0.4	54	22.3
	F....	10	4.1	4	1.6	..	..	..	..	1	0.4	15	6.2
55–64	M...	12	4.9	9	3.7	8	3.3	1	0.4	..	..	30	12.3
	F....	14	5.7	9	3.7	9	3.7	1	0.4	..	..	33	13.4
65 and over	M...	12	4.9	10	4.1	6	2.4	2	0.8	..	..	30	12.3
	F....	4	1.6	4	1.6	2	0.8	1	0.4	1	0.4	12	4.9
Total.....		130	53.3	57	23.2	40	15.9	11	4.5	5	2.1	243	100

to one-half diameter or reduction of one coronary artery to a bore of less than half over an aggregate distance of $^1/_2$ inch.

Grade 5: Disease greater than the above, e.g., frank closure of one coronary ostium or occlusion of one major vessel.

When disease is present in more than one of the major coronary arteries or in both the ostia and arteries, the total effect must be calculated to fit the aforementioned classification; another drawback in this classification is that it does not take into account the effect of any anastomotic blood supply which may be present. Grade 2 would be "mild" disease, grade 3 would be "moderate" disease and grades 4 and 5 would be "severe" disease.

Incidence of Coronary Atherosclerosis in the Bantu: Of 306 patients who reached puberty, sixty-three were under thirty-five years of age. With one very important exception, none of the sixty-three showed any significant coronary atherosclerosis. The detailed tabulation (Table IV) is therefore limited to the remaining 243 patients over the age of thirty-four years. The important exception in the younger age groups was a twenty-two year old Bantu man who died of myocardial infarction.

As found previously with the aorta and the cerebral arteries of the Bantu,[19] the coronary arteries show no immunity to atherosclerosis. Twenty-three per cent of the patients over thirty-four years of age showed a marked degree of atherosclerosis; almost half of the 243 in this group showed coronary atherosclerosis of some degree.

Our findings on the incidence of coronary atherosclerosis in the South African Bantu fall midway between the figures for the Bantu and for the United States population as given by Higginson and Pepler.[16]

Effect of Coronary Sclerosis on the Myocardium of the Bantu: Of the 306 patients over fourteen years of age, twelve showed the following lesions: rheumatic myocarditis, three patients; tuberculous myocarditis, one patient; isolated myocarditis (Fiedler), four patients; Becker's cardiac collagenosis, four patients.

These twelve patients have been excluded from the detailed study (Table V). The incidence of Becker's collagenosis found by us is somewhat less than the latest figures quoted by him.[2] None of the patients in our series showed the endomyocardial sclerosis reported originally by Bedford and Konstam[3] as being not rare in other parts of Africa. Like Becker, we regard this condition as being very rare in South Africa.

In the remaining 294 patients the one histopathological change in the heart which overshadowed all others was "patchy ischaemic fibrosis."

A recheck of the sections of damaged heart muscle was possible in 149 necropsy cases; these can be summarized as follows:

TABLE V

Incidence of Patchy Fibrosis of Heart in 294 Patients over Fourteen Years of Age*

Cardiac Disease	Degree of Patchy Fibrosis in Heart								Total	
	None		Mild or Isolated		Severe		Frank Infarct		No.	%
	No.	%	No.	%	No.	%	No.	%		
No apparent disease of valves or coronary arteries; no myocardial hypertrophy	134	45.6	5	1.7	1	0.34	..	..	140	47.6
Valvular disease, aortic and/or mitral	5	1.7	6	2.0	2	0.7	1	0.34	14	4.8
Myocardial hypertrophy										
Pure, no coronary disease	19	6.4	21	7.1	7	2.4	..	..	47	16.0
With coronary sclerosis	4	1.3	15	5.1	9	3.0	2	0.7	30	10.2
Coronary atherosclerosis										
Grade 2	12	4.1	11	3.7	1	0.34	..	..	24	8.1
Grade 3	5	1.7	12	4.1	8	2.7	..	..	25	8.5
Grades 4 and 5	3	1.0	1	0.34	3	1.0	2	0.7	9	3.0
Miscellaneous	3	1.0	2	0.7	..	..	..	..	5	1.7
Total	185	62.8	73	24.9	31	10.5	5	1.7	294	100

* Twelve patients are excluded from the original total of 306 patients. Percentage incidences are based on a total of 294 patients. A diagnosis of hypertrophy of the heart is based on heart weight and thickness of the ventricles[7] together with microscopic findings in the heart and kidneys. In six of the thirty patients with cardiac hypertrophy and coronary atherosclerosis, hypertrophy was probably secondary to the coronary artery disease.[5,12]

Forty-two cases: No fibrosis or other significant pathologic condition.

Seventy-seven cases: Isolated foci of fibrosis, often perivascular in distribution but occasionally severe and of doubtful significance as to etiology.

Twenty-six cases: Patchy foci of fibrosis, mainly perivascular in distribution. Most of these foci were in the inner half of the heart wall and many were associated with myocardial hypertrophy. There was no evidence of rheumatic carditis or any other active inflammatory lesion. These cases are consistent with an ischemic fibrosis (Figs. 2 and 3).

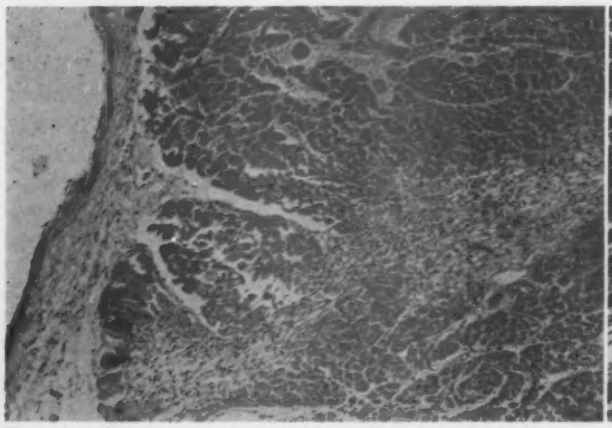


FIG. 2. Low power view of patchy fibrosis in heart muscle.

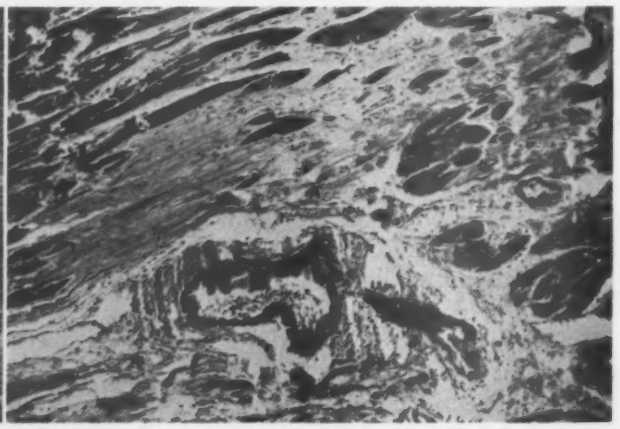


FIG. 3. High power view of patchy fibrosis in heart muscle.

Four cases: Areas of extensive fibrosis considered to be areas of previous infarction with subsequent fibrosis.

Other workers have reported patchy fibrosis in the hearts of the Bantu.[1,13,15] Harrison and Wood[12] also had noted similar ischemic changes in hearts from European patients with hypertension or coronary sclerosis. The changes which were termed "focal fibrosis" were considered to be the result of occlusion of small vessels and they concluded "these are minute infarcts."

Table V shows the relationship between the incidence of this patchy fibrosis and the findings of cardiac disease in our series. With two exceptions, patchy fibrosis in the heart has been reported to be present only in those cases in which the original histopathologic report on the heart is in agreement with our later review of the same material.

Table V shows that this patchy myocardial fibrosis was found in only 4 per cent of "normal" hearts; each time the lesion was minimal. In striking contrast, in conditions known to cause myocardial ischemia, i.e., valvular disease, hypertrophy and coronary atherosclerosis,[4,5,17] the incidence of this lesion is not only much higher but also becomes increasingly severe and common as the severity of the related lesion increases.

Comments

By the hemodynamic law of Poiseuille,[30] "with constant pressure the flow in a tube varies as the fourth power of the diameter," necessarily any narrowing of the coronary bore, provided it is over a significant proportion of the vessel length, must interfere with the blood supply to the myocardium. In Table IV it has been shown that narrowing of the coronary ostia and/or the coronary arteries is not uncommon in the Bantu, sometimes being found in severe degree. It would therefore be most strange if the myocardium of such patients did not suffer. Yet there seems broad agreement that gross myocardial infarction is rare in the Bantu. Higginson and Pepler[16] found in autopsies on Bantu patients with cardiac disease that only 0.6 per cent showed frank infarcts. Schrire,[28] in studying a small series of hospital outpatients over the age of nineteen years, found clinical evidence of myocardial infarction in 10.3 per cent of Europeans but only in 0.3 percent of Bantus. Schwartz et al.,[29] in a series of 275 Bantu hospital inpatients with cardiac disease, found the incidence of probable myocardial infarction under 0.4 per cent. In our autopsy series the incidence is higher, namely, five cases of frank infarction in 306 consecutive autopsies performed on persons over fourteen years of age (1.5 per cent). The autopsy findings are in keeping with the clinical findings, in which three definite and three probable cases of myocardial infarction were found in a series of 206 Bantu inpatients with cardiac disease; this gives an incidence of 1.4 per cent definite and additionally 1.4 per cent probable. Necessarily there is an overlap in the autopsy and clinical material.

Even this higher incidence found by us is quite unlikely to be the whole truth. Allowance must be made for the fact that this is a land of great distances, with few doctors in the outlying areas, a poor population and no death certification for the rural Bantu. Under such circumstances there is little likelihood that the large majority of Bantu patients with an acute grave cardiac condition would reach a hospital or even have the cause of death recorded.

Nevertheless, there seems little doubt that the incidence of *gross* myocardial infarction is much lower in the South African Bantu than in the European. Gross myocardial infarction, however, is only one trade-mark of myocardial ischemia.

The difference between patchy ischemic fibrosis and gross infarction is only one of degree since such patchy areas are minute infarcts.[12]

Myocardial scars are late phenomena and may give little indication of whether the original damage was to the interstitial tissue of the heart, as in rheumatic myocarditis, or whether the parenchyma itself was the site of damage, as in ischemia or diphtheria. Several conditions with a similar picture microscopically include not only ischemic fibrosis but also rheumatic carditis, syphilis, glycogen storage disease, amyloidosis, hemochromatosis, Fiedler's myocarditis, beriberi, familial cardiomegaly of Evans and Coxsackie disease.[5,15] It has been possible to identify and exclude the more common conditions such as rheumatic carditis; the others listed are "mostly obscure and relatively rare" and could not explain anything more than a fraction of the patchy fibrosis found in this series. Higginson, Gillanders and Murray[15] did suggest chronic malnutrition as a cause of patchy fibrosis of the myocardium in a series of twelve Bantu patients dying of cardiac disease of unknown etiology, but their

patients were of good physique and had hypertrophied hearts. Schwartz et al.[20] from the same area do not accept malnutrition as the likely explanation of their "cryptogenic" group of Bantu patients with cardiac disease. Similarly, we would not accept this theory of malnutrition as likely to apply to our patients with patchy myocardial fibrosis. At autopsy we see much malnutrition at the extremes of life but have never established any relationship between malnutrition and patchy myocardial fibrosis.

To clarify this problem we classified the cardiac lesions found in 207 patients under fifteen years of age at the time of death. Of this pathetic group no less than 42 per cent died of undernutrition or malnutrition, yet in the whole group of 207 only four patients showed patchy myocardial fibrosis. Of these four, only one fell into the group of 42 per cent with nutritional disorders. The same lack of relationship is found in malnourished patients at the other extreme of life.

From the relationship of the patchy myocardial lesion with cardiac disorders known to cause myocardial ischemia we would suggest that at least in the majority of our patients showing this patchy fibrosis in the heart, the condition is due to myocardial ischemia. This view is supported by the findings in the clinical study, especially as regards the patients with cryptogenic heart disease, e.g., the electrocardiographic tracings suggest a myocardial lesion and the angina pectoris suggests ischemia of the myocardium.

It is suggested that the South African Bantu has no freedom from or immunity to coronary atherosclerosis or to coronary heart disease. He differs only from the Europeans in that he much less commonly presents with gross myocardial infarction and sudden death. In the Bantu the more common mode of onset of ischemic myocardial disease would seem to be by minute infarcts which cause patchy fibrosis of the myocardium and resultant cardiac failure. One possible explanation is that the Bantus do not readily develop clotting in the main coronary branches, i.e., the ischemia of the myocardium is due to a simple cutting down of the blood flow by atherosclerosis of the coronary arteries or narrowing of the ostia. Gillman et al.,[10] from their extensive work with the Bantu of South Africa, state "the fibrinolytic capacity of plasma seems to be higher in Africans than Europeans and especially in Africans with liver disease. The possibility exists that the latter pathology may, by elevating the plasma fibrinolytic enzymes, decrease significantly the African's susceptibility to coronary intimal deposits and/or thrombosis even in the face of both elevated plasma-fibrin levels and the existence of coronary artery pathology. . . . Our findings would seem to indicate, as suggested earlier by Woods and Laurie, that the rarity of coronary occlusive episodes is not attributable solely to the lowered incidence of coronary artery pathology among this people nor yet to their low blood lipids but rather to other associated metabolic conditions."

Summary

The results are reported of a clinicopathologic investigation into three problems of cardiac disease in the South African Bantu: (1) the incidence of coronary atherosclerosis in the Bantu; (2) the effect of any such coronary atherosclerosis on the myocardium of the Bantu; (3) the problem of the large number of Bantu patients with cardiac disease reported as suffering from clinically unidentified heart disease, i.e., the so-called "cryptogenic" group of cardiac patients.

The material consisted of 206 consecutive cardiac patients admitted to the Edendale Hospital medical wards over a six-month period, and of 513 necropsies specially investigated of a total of 1,048 autopsies performed at Edendale Hospital from June 1957 to June 1958.

The postmortem material showed that coronary atherosclerosis does occur in the Bantu and is sometimes found in severe degree. The clinical findings were in agreement, e.g., the presence of myocardial ischemia in the cardiac patients was shown by the finding that angina pectoris was a not uncommon presenting symptom.

In the postmortem and clinical series the incidence of proved frank myocardial infarction in the Bantu was about 1.4 per cent, an incidence higher than that reported by other workers but much lower than that in European patients.

Histopathological examination of the autopsied hearts showed patchy fibrosis was a common finding in the myocardium of the Bantu dying of heart disease. There was a close relationship between the incidence and severity of patchy fibrosis and coronary atherosclerosis. The hearts of Bantu patients with cardiac disease suffering from occlusive disease of the coronary arteries

and/or the ostia do not commonly present with gross frank myocardial infarction but rather with minute infarcts. A suggested explanation is advanced to account for this difference between Bantu and European patients suffering from coronary heart disease.

It is suggested that the so-called "cryptogenic" group of Bantu cardiac patients consists largely of undiagnosed examples of well recognized causes of heart disease, notably coronary heart disease, decompensated hypertension and pericardial disease.

References

1. Becker, B. J. P. Cardiovascular disease in the Bantu and coloured races of South Africa. *South African J. M. Sc.*, 2: 1, 97, 1946.
2. Becker, B. J. P. In: Some African cardiopathies. Report of a joint seminar of the Departments of Pathology and Medicine of the University of the Witwatersrand. *South African M. J.*, 31: 686, 1957.
3. Bedford, D. E. and Konstam, G. L. Heart failure of unknown aetiology in Africans. *Brit. Heart J.*, 8: 236, 1946.
4. Blumgart, H. L., Schlesinger, M. J. and Davis, D. Studies on the relation of the clinical manifestations of angina pectoris, coronary thrombosis and myocardial infarction to the pathological findings. *Am. Heart J.*, 19: 1, 1940.
5. Brigden, W. Uncommon myocardial diseases. The non-coronary cardiomyopathies. *Lancet*, 2: 1179, 1243, 1957.
6. Bronte-Stewart, B., Keys, A. and Brock, J. F. Serum cholesterol, diet and coronary heart disease. *Lancet*, 2: 1103, 1955.
7. Coggin, C. B., Griggs, D. E. and Stilson, W. L. The heart in pneumoconiosis. *Am. Heart J.*, 16: 411, 1938.
8. Fishberg, A. M. Hypertension and Nephritis, 5th ed. Philadelphia, 1954. Lea and Febiger.
9. Gelfand, M. The Sick African. 1944. Stewart Printing Co.
10. Gillman, T., Naidoo, S. S. and Hathorn, M. Fat, fibrinolysis and atherosclerosis in Africans. *Lancet*, 2: 696, 1957.
11. Grusin, H. and Dando, R. V. Myocardial infarction in a South African Bantu. *Med. Proc.*, 2: 290, 1956.
12. Harrison, C. V. and Wood, P. Hypertensive and ischaemic heart disease: A comparative clinical and pathological study. *Brit. Heart J.*, 2: 205, 1949.
13. Higginson, J. In: Some African cardiopathies. Report of a joint seminar of the Departments of Pathology and Medicine of the University of the Witwatersrand. *South African M. J.*, 31: 855, 1957.
14. Higginson, J. Geographical pathology of geomedicine in South Africa. *Med. Proc.*, 4: 268, 1958.
15. Higginson, J., Gillanders, A. D. and Murray, J. F. The heart in chronic malnutrition. *Brit. Heart J.*, 14: 213, 1952.
16. Higginson, J. and Pepler, W. J. Fat intake, serum cholesterol concentration and atherosclerosis in the South African Bantu. II. Atherosclerosis and coronary artery disease. *J. Clin. Invest.*, 23: 1366, 1954.
17. Horn, H., Field, L. E., Dack, S. and Master, A. M. Acute coronary insufficiency: Pathological and physiological aspects. *Am. Heart J.*, 40: 63, 1950.
18. Hunter, W. S. Coronary occlusion in Negroes. *J. A. M. A.*, 131: 12, 1946.
19. Laurie, W. and Woods, J. D. Atherosclerosis and its cerebral complications in the South African Bantu. *Lancet*, 2: 231, 1958.
20. Laurie, W. and Woods, J. D. Anastomosis in the coronary circulation. *Lancet*, 2: 812, 1958.
21. Mann, G. V. The epidemiology of coronary heart disease. *Am. J. Med.*, 23: 463, 1957.
22. Morris, J. N. Recent history of coronary disease. *Lancet*, 1: 69, 1951.
23. Paton, B. C. The accuracy of diagnosis of myocardial infarction. A clinicopathologic study. *Am. J. Med.*, 23: 761, 1957.
24. Price, F. W. Text Book of the Practice of Medicine, 7th ed. London, 1955. Oxford University Press.
25. Reid, D. D. The epidemiology of coronary disease. *Practitioner*, 180: 184, 1958.
26. Rosenberg, D. M. L. Cardiac revascularisation in coronary artery disease. *South African M. J.*, 32: 686, 1958.
27. Schrire, V. and Uys, C. Cardiac infarction in the Bantu. *Am. J. Cardiol.*, 2: 453, 1958.
28. Schrire, V. Myocardial infarction. Its racial incidence in Cape Town during 1956. *South African M. J.*, 32: 177, 1958.
29. Schwartz, M. B., Schamroth, I. and Seftel, H. C. The pattern of heart disease in the urbanised (Johannesburg) African. *Med. Proc.*, 4: 275, 1958.
30. Vowles, K. D. J. and Howard, J. M. Myocardial and cerebral infarctions as post-operative complications. *Brit. M. J.*, 1: 1096, 1958.
31. Wanscher, O., Clemmesen, J. and Nielsen, A. Negative correlation between atherosclerosis and carcinoma. *Brit. J. Cancer*, 5: 172, 1951.
32. White, P. D. Heart Disease, 4th ed. New York, 1951. The Macmillan Co.
33. Wigle, E. D. Myocardial fibrosis and calcareous emboli in valvular heart disease. *Brit. Heart J.*, 19: 539, 1957.

Problem of Heart Disease in India*

K. S. MATHUR, M.D., M.R.C.P.

Agra, India

HEART disease is a world problem but there are differences between peoples and regions in regard to the burden and kind of heart disease afflicting them. These may in some way be related to the different ways of life including race, climate, type of work, stress and strain, local customs as well as diet. International epidemiologic cardiovascular research therefore aims at collecting information about the most important causes of heart disease and the incidence and severity of their effects on the heart under different conditions and in every corner of the globe.

Statistics from surveys, not only from hospital clinics and private practice but also from entire communities, have slowly accumulated from many countries of the West but comparable studies from India are lacking. We need a large well organized nation-wide study of morbidity and mortality from heart disease. Until that time, we must depend on isolated studies of different population groups in our country. Several such statistical surveys of the incidence of heart disease have been published.[1-6] They are based on an analysis of case records of patients admitted to the general wards of hospitals usually under the care of different physicians, covering a period of from one to five years. These hospitals invariably cater to people belonging to low socioeconomic groups with a sprinkling of middle class.

This paper is based on a review of the Indian literature and personal observations extending over a period of twelve years among hospital and private patients with respect to the incidence of heart disease and the frequency of different etiologic forms.

MATERIAL

The present investigations were made at Agra, which is one of the two big medical centers in Uttar Pradesh, the biggest state of India. The patients are drawn not only from the rural and urban population of Agra but also from most of the surrounding western districts of the state. The climate is hot and dry during summer, cold during winter and humidity is marked only during the monsoon months.

This study includes both hospital and private patients. The bulk of the former is made up of farmers, industrial labourers, domestic and office servants, clerks and petty businessmen; whereas professionals, business executives and government officials make up the majority of private cases. The material is, therefore, representative of low, middle and upper socioeconomic groups and is drawn from both rural and urban areas.

All the private and most of the hospital cardiac patients were under my direct charge, thus ensuring uniformity of diagnostic skill and etiologic typing.

During the twelve-year period under review (January 1946 to August 1957), 27,502 patients were admitted to the medical wards of the Sarojini Naidu Hospital, Agra. Of the total medical admissions 2,145 were patients with organic heart disease. During the same period 1,127 cardiac patients were seen in private consultant practice. A total of 3,272 patients suffering from heart disease are thus available for study.

INCIDENCE

The diagnosis of organic cardiovascular disease was made in 2,145 of 27,502 patients admitted to the medical wards of the Sarojini Naidu Hospital, an incidence of 7.7 per cent. The incidence in the private series of cases will be fallacious as it depends so much on the individual physician with his own bias for speciality.

Etiologic Classification: The etiologic factor or factors responsible for heart disease could be ascertained in 3,010 or 92 per cent of the total 3,272 cases (Table I). The etiology remained obscure in the remaining 262 or 8 per cent of cases (10.2 per cent of hospital and 3.8 per cent of private cases).

This analysis includes cases in which more than one etiologic factor was concerned in the development of cardiac disease, e.g., 278 of 553

* From the Cardiovascular Research Unit, Sarojini Naidu Medical College, Agra, India.

TABLE I
Incidence of Different Etiological Groups Amongst 3,272 Cardiac Cases

Type of Heart Disease	Total Cases		Hospital Cases		Private Cases	
	No.	%	No.	%	No.	%
Rheumatic	1,027	31.3	809	37.8	218	19.5
Hypertensive	607	18.5	297	13.8	310	27.4
Coronary	553	16.9	152	7.0	401	35.2
Cor pulmonale	467	14.3	410	19.2	57	5.2
Congenital	106	3.3	57	2.6	49	4.5
Syphilitic	73	2.3	55	2.5	18	1.6
Subacute bacterial endocarditis	45	1.3	30	1.4	15	1.4
Miscellaneous	132	4.0	116	5.5	16	1.4
Unknown	262	8.0	219	10.2	43	3.8

patients with coronary heart disease had hypertension and 42 of 45 patients with subacute bacterial endocarditis had chronic rheumatic endocarditis. Multiplicity of etiologic factors is an important fallacy in statistically analysing and attributing to one cause a disease which is due to several causes.

Age Distribution: The percentage distribution of cases of organic heart disease has been worked out per decade according to the various etiologic types (Table II).

It will be observed that in the earlier decades of life congenital and rheumatic heart disease play a predominant role, whereas a sudden rise in the incidence of hypertension, coronary heart disease and chronic cor pulmonale occurs in middle age, especially after forty years.

Etiologic Forms

Rheumatic Heart Disease

Western writers have repeatedly denied the existence of rheumatic heart disease in the tropics. This unfortunate impression was created by Rogers[7] who reported only one case of rheumatic carditis in 4,800 autopsies performed in Calcutta over thirty-seven years and came to the conclusion that although heart disease occurs with fair frequency in India, rheumatic endocarditis is quite absent. Since then, numerous papers from all over the country have established that rheumatic heart disease is the most important cause of heart disease in India. Its incidence varies from 20.2 per cent of all cardiac cases in Amitsar[5] to 24.8 per cent in Bombay,[8] 39.1 per cent in Delhi[6] and 46.8 per cent in Madras.[2] The highest incidence has recently been reported by Devi Chand[9] from Himalayan ranges in Simla (Himachal Pradesh) where 50.6 per cent of the total cardiac cases belonged to the rheumatic group. Another interesting observation was made in our research laboratories by Wahi

TABLE II
Age Distribution of Cardiac Cases (Figures Expressed in Percentage)

Type of Heart Disease	Total No.	Age Group (yr.)									
		0–10	11–20	21–30	31–40	41–50	51–60	61–70	71–80	81–90	91–100
Rheumatic	1,027	11.5	40.3	25.2	16.0	4.9	2.1	—	—	—	—
Hypertensive	607	—	3.7	7.5	18.0	30.0	25.5	13.6	1.5	—	0.2
Coronary	553	—	0.1	2.5	9.8	30.5	34.3	18.6	3.9	0.3	—
Cor pulmonale	467	—	2.3	9.5	25.6	37.1	21.3	3.7	0.5	—	—
Congenital	106	54.8	22.6	16.6	4.8	1.2	—	—	—	—	—
Syphilitic	73	—	—	9.2	37.3	27.7	20.3	1.8	3.7	—	—
Subacute bacterial endocarditis	45	10.5	26.3	34.2	21.1	7.9	—	—	—	—	—
Miscellaneous	132	3.5	9.7	13.2	16.9	18.6	15.0	18.6	3.6	0.9	—
Unknown	262	0.7	8.5	15.0	21.3	24.1	17.0	11.3	1.4	0.7	—

and Samuel[10] when they reported stigmas usually considered to be characteristic of rheumatic fever, mostly in proximity to the mitral valve, in 56 per cent of hearts examined at autopsy from patients in whom previous rheumatic infection could be easily ruled out.

An analysis of our own series of cardiac cases showed that 37.8 per cent of hospital patients and 19.5 per cent of private patients suffered from rheumatic heart disease, with an over-all incidence of 31.3 per cent among 3,272 cardiac patients. Males were more commonly affected than females in the ratio of 2.4:1. Mean age of the rheumatic group was 22.3 years with peak incidence in the second and third decades of life. Only 7 per cent of patients were over forty years of age.

Mitral stenosis was the most common valvular lesion. As an isolated structural valvular disease, it was diagnosed in 24.2 per cent of cases, but when considered along with other valvular defects, its incidence was 81.5 per cent of rheumatic heart disease. Mitral regurgitation was present in 56.6 per cent, aortic incompetence in 15.1 per cent and aortic stenosis in 2.6 per cent of cases, alone or in combination with other valvular lesions. Acute rheumatic carditis was recorded in 4.1 per cent of cases. Cases of rheumatic fever without cardiac involvement have been excluded from the present study, but it is worth recording that rheumatic nodules were extremely rare as a manifestation of rheumatic activity. The incidence of chorea was as low as 1.5 per cent.

Cardiac failure was associated with rheumatic heart disease in 79.5 per cent of cases and auricular fibrillation in 10.5 per cent, although in a study of 200 consecutive cases of auricular fibrillation[11] 75 per cent had rheumatic endocarditis.

HYPERTENSIVE HEART DISEASE

There has been speculation based on unconfirmed reports by some investigators in the United States that arterial hypertension in the absence of renal disease is uncommon or rare in certain Oriental countries, particularly in India and China. Schroeder[12] recently made a personal survey in the principal cities of seven countries and came to the conclusion that hypertension was present in all places in India and that it was quite common in the Chinese of Formosa, Hongkong and Manila but not as common as in Japan. Gunewardene[1] reported hypertensive heart disease in 13 per cent of hospital patients and 25 per cent of private patients with cardiovascular disease. Sen Gupta,[13] in an analysis of cardiac cases in Calcutta, found the incidence of hypertensive heart disease to be 7.8 per cent in 1931 and 18.3 per cent in 1935. According to Kutumbiah,[14] heart disease in 16 per cent of patients treated at King George Hospital, Vizagapatam, South India, was due to high blood pressure. Among hospital patients the incidence of hypertensive heart disease was regarded as 29 per cent by Vakil[15] at Bombay, 25.4 per cent by Malhotra[5] at Amritsar and 21.1 per cent by Padmavati[6] at Delhi.

Hypertensive heart disease is the second most important group of cardiovascular diseases in India. It accounted for 13.8 per cent of my hospital patients and 27.4 per cent of my private patients. The over-all incidence of 18.5 per cent recorded in Table I will rise to 27 per cent if correction is made by inclusion of 278 other hypertensive patients in this group, who presented with symptoms of coronary heart disease and have been considered under that head. It is more commonly observed in males than females in the ratio of 3:1. Highest incidence was found in the fifth and sixth decades; only 11.1 per cent of patients were under thirty years of age.

The heart is much more commonly involved than the brain in cases of hypertension in India, whereas cerebral hemorrhage is the principal fatal consequence of hypertension in Japan.[12] In my series of patients, 84.1 per cent had primary benign hypertension, 11.4 per cent malignant hypertension and 4.5 per cent had hypertension of renal origin.

Field surveys among rural and urban population of Uttar Pradesh during the last three years have failed to link the frequency of hypertension to the intake of a specific amount or kind of dietary fat, protein or salt.

CORONARY HEART DISEASE

There is worldwide interest in coronary heart disease. Justifiably regarded as the top-ranking public health problem in the United States, it is being recognised as an important cause of cardiovascular disease in India. Vakil[4] reported an incidence of 13.5 per cent in his hospital series, but on extending a similar inquiry to heart cases in private practice he found the frequency of coronary heart disease much higher,[16] viz. 26 per cent. Statistical analyses published from different parts of the country record an incidence of 13 per cent in

Madras,[2] 23.4 per cent in Amritsar[17] and 13.3 per cent in Delhi.[6]

Our own observations during the last two decades in hospital and consultant private practice have convinced us that the incidence of coronary heart disease in India is on the increase. We have also drawn attention to cases of asymptomatic myocardial infarction[18] and the possibility of coronary occlusion syndrome in acute falciparum malaria.[19]

In the present series of 3,273 cardiac patients, there were 553 cases of coronary heart disease, accounting for 16.9 per cent of all cardiac cases. The incidence was as high as 35.2 per cent among private cases; 89 per cent were males and 11 per cent females. Although males outnumbered females in the ratio of 8:1, the difference was less marked beyond the age of forty-five years. The peak age incidence was forty-five to fifty-five years, and two-thirds of all patients were between forty to sixty years old. We have also observed the recent increase in the frequency of coronary heart disease in younger age groups; 12.3 per cent of our patients were under forty years and the youngest was eighteen years old.

People belonging to upper socioeconomic strata of society formed 63.3 per cent of these patients; 25 per cent came from middle class and 11.7 per cent from low socioeconomic groups. These statistical data have found further confirmation from the field surveys of the incidence of coronary heart disease in different socioeconomic groups of the general population in which we have been engaged during the last three years. Of all these patients 88.2 per cent lived in towns and 11.8 per cent in rural areas. 26.9 per cent were smokers and 11.2 per cent took alcohol moderately.

Hypertension was associated with uncontrolled diabetes in 13 per cent and the serologic test for syphilis was positive in 3.8 per cent of these patients. A family history of coronary heart disease was available in 7.4 per cent, hypertension in 3.8 per cent and diabetes in 2 per cent of cases only; these figures may be considered as underestimates, as most of the patients did not know the actual cause of death of their family members or the latter had been treated by persons practising indigenous systems of medicine, who were ignorant of these diseases.

The question of vegetarian versus non-vegetarian diet frequently arises; 62.2 per cent of patients of our series were vegetarian and 37.8 per cent non-vegetarian. But this question is unimportant as with few exceptions the so-called non-vegetarian in India takes meat two or three times a week. We have, therefore, studied the nutritional status and blood lipids of 100 consecutive patients with coronary heart disease. We have compared these with similar studies on 816 unselected healthy persons from the general population.[20] We have found that patients with coronary heart disease consumed total amounts of fat and fat calories comparable to those of the high socioeconomic groups of the general population which bear the maximum burden of coronary heart disease. The mean values of total serum cholesterol and phospholipids in patients with coronary heart disease were even higher than those of high socioeconomic groups which were the highest in the field study of the normal population.

Included among the 553 cases of coronary heart disease were cases of myocardial infarction (71 per cent), angina pectoris (24 per cent) and coronary failure (5 per cent). The maximum number of attacks of acute myocardial infarction were precipitated during the winter months and rainy season.

PULMONARY HEART DISEASE

According to the majority of Western statistical studies, pulmonary heart disease accounts for but a small percentage of cases of cardiovascular diseases. In India, Vakil[4] observed an over-all incidence of chronic cor pulmonale of 10 per cent of all heart cases admitted to K.E.M. Hospital, Bombay. Raman,[3] on the other hand, estimated that only 0.4 per cent of the cardiac patients admitted to Vizagapatam Hospital suffered from pulmonary heart disease. Padmavati[6] reported an incidence of 16.6 per cent from Delhi.

The conflicting opinions on the incidence of cor pulmonale may be due to different criteria used in the diagnosis, but careful clinical studies have convinced us that chronic cor pulmonale is much more common than most statistical surveys have indicated. The statistical data of the two biggest medical centers in our state of Uttar Pradesh indicate that the incidence in our state is the highest in India. Bhatia and Jain[21] reported an incidence of 18.5 per cent amongst patients admitted to G. M. Hospital, Lucknow, whereas 19.2 per cent of the cardiac patients admitted to S. N. Hospital, Agra suffered from chronic pulmonary heart disease.

A high preponderance of chronic cor pul-

monale has been reported among men;[22] 69.7 per cent of our series were males and 30.3 per cent females. Males suffered from pulmonary heart disease twice as commonly as females but the difference was most apparent in the sixth decade when men were affected seven times more commonly than their opposite sex. It was in the early age group below thirty years that the number of men and women was about equal. The mean age in the present series was 45.1 years; the oldest patient suffering from chronic bronchitis and emphysema was aged eighty years and the youngest was a female patient aged sixteen years suffering from pulmonary tuberculosis. Although the peak incidence was in the fifth decade, 81 per cent patients were between thirty-one and sixty years old.

Chronic bronchitis with emphysema was the predominant factor in the causation of chronic cor pulmonale, being responsible for 85.3 per cent of all cases. Bronchial asthma was the cause in 7.2 per cent and pulmonary tuberculosis in 5.1 per cent. It is interesting to note that among 1,988 consecutive cases of pulmonary tuberculosis admitted to the hospital during the same period, chronic cor pulmonale was found in 0.9 per cent. Bronchiectasis was the etiologic factor in 2 per cent and pulmonary fibrosis with atelectasis in 0.2 per cent of cases.[22]

CONGENITAL HEART DISEASE

There has been a notable increase in the reported incidence of congenital heart diseases all over the world, depending on the facilities for diagnosis and surgical treatment available at those centers. In an analysis of cardiovascular patients attending the hospital at Delhi recently, Padmavati[6] observed that 4.8 per cent of patients suffered from congenital heart diseases. Vakil[4] had reported an incidence of 1 per cent from Bombay in 1948.

The diagnosis of congenital heart disease was made in 3.3 per cent of cardiac cases I saw at Agra. More than half the patients were under ten years of age and 94 per cent were under thirty years of age. The cases included Fallot's tetralogy (24.5 per cent), patent ductus arteriosus (15.2 per cent), interventricular septal defect (17.9 per cent), interauricular septal defect (10.4 per cent), pulmonary stenosis (6.6 per cent), aortic stenosis (6.6 per cent), dextrocardia (2.8 per cent), tricuspid atresia (0.9 per cent) and bicuspid aortic valve (0.9 per cent). In the remaining 14.2 per cent a definite diagnosis could not be arrived at by the diagnostic methods available to us.

SYPHILITIC HEART DISEASE

Syphilitic heart disease, which at one time was the second most common and important cause of infective cardiovascular disease, is becoming increasingly uncommon in our country. The highest incidence of 12.9 per cent was report d by Vakil from Bombay in 1948.

During the twelve-year period under review, cardiovascular syphilis accounted for only 2.3 per cent of cases. This figure could be further reduced if only the statistics of the last five years are taken into account. The patients ranged in age from twenty-two to seventy-six years; of these 85.3 per cent were between thirty-one and sixty years. Maximum incidence was in the fourth decade; only 9.2 per cent were under thirty years and 5.5 per cent over sixty years. It was predominantly a disease of males. The clinical manifestations of syphilitic heart disease were aortic incompetence, aneurysm of the aorta and angina, in that order of frequency.

SUBACUTE BACTERIAL ENDOCARDITIS

The incidence of subacute bacterial endocarditis has been variously reported in the literature. It was 1.3 per cent in the present series. The highest incidence of 34.2 per cent was in the third decade, 10.5 per cent were below ten years and 7.9 per cent in the fifth decade. It was superimposed on chronic rheumatic endocarditis in 93.3 per cent and on congenital heart disease in the remaining 6.7 per cent of cases.

MISCELLANEOUS AND UNKNOWN GROUP

Cases of diverse etiology, such as tuberculous pericarditis, thyrotoxicosis, anemia, beri beri, epidemic dropsy, acute infection and trauma, accounted for 4 per cent of cardiovascular patients under review.

There still remained 8 per cent of patients who presented with definite structural changes in the heart or evidence of disturbed cardiac function and in whom no definite etiologic factor or factors could be determined. It is possible that some of the cases marked "unknown" were cases of asymptomatic coronary heart disease, masked hyperthyroidism, beriberi, or undiagnosed hypertensive heart disease where the blood pressure had fallen with the onset of

congestive heart failure. But one is left with the impression that there exist in the tropics other cases of "nutritional heart disease," which so far have not been defined and recognised as clinical entities.

Conclusions

As a contribution to international knowledge of the epidemiology of heart disease, the data on the frequency of heart disease in India have been presented. The data include those derived from a survey of the Indian literature and from a series of 3,273 cardiac patients seen in hospital and private practice by me.

Rheumatic heart disease still heads the list of cardiovascular diseases in India in the hospital class of patients. The conquest of rheumatic heart disease will take much effort in our country but we can be optimistic about the outcome at some future date.

Hypertensive and coronary heart diseases still account for the majority of private cases, which belong to upper and middle socio-economic groups. The increasing incidence of these so-called degenerative heart diseases is a great challenge. The only hope confronting us lies in the simple fact that their incidence and mortality are not the same in different populations and different countries.

The incidence of pulmonary heart disease is surprisingly high in our series when compared to the statistical data from other parts of the world and even from other parts of India. We venture to suggest that the high incidence of chronic cor pulmonale in Uttar Pradesh may be due to extreme variations of temperature, dust and the habit of flocking around a fire with excessive smoke during winter, all accounting for frequent attacks of cough among the hospital class of patients who do not take treatment in the early stages.

The increase in the frequency of congenital heart disease is due to more accurate diagnosis and the availability of adequate surgical treatment. The latter draws patients to the hospital who never sought help before.

Syphilitic heart disease is declining to the point where it soon will be only of historic interest.

It is suggested that some of the cases of heart disease in which the etiology remains obscure are due to nutritional changes in the heart, which have not so far been clearly defined and may in the future form a group of "nutritional heart diseases."

References

1. Gunewardene, H. O. Heart Disease in the Tropics, Calcutta, 1935. Butter Worth & Co.
2. Sanjivi, K. S. Heart disease in South India. In: Proceedings of the Annual Conference of Association of Physicians of India, 1946.
3. Raman, T. K. Heart disease in Vizagapattam. In: Proceedings of the Annual Conference of Association of Physicians of India, 1947.
4. Vakil, R. J. An aetiological study of the heart diseases in Bombay. *Indian J. M. Sc.*, 2: 465, 1948.
5. Malhotra, R. P. Cited by Padmavati, S.[6]
6. Padmavati, S. Five year survey of heart disease in Delhi, *Indian Heart J.*, 10: 33, 1958.
7. Rogers, L. and Megaw, J. W. D. Tropical Medicine. London, 1939. J. & A. Churchill Ltd.
8. Vakil, R. J. A study of rheumatic heart disease in Bombay Province (India). *Indian Heart J.*, 1: 15, 1949.
9. Devi Chand. Etiology and epidemiology of rheumatic fever and rheumatic heart disease. *Agra M. Coll. J.*, 10: 25, 1958.
10. Wahi, P. N. and Samuel, K. C. The incidence of rheumatic stigmata in heart in Indians. *Indian Heart J.*, 3: 1, 1951.
11. Mathur, K. S. Common arrhythmias and their management. *Licentiate*, 5: 385, 1956.
12. Schroeder, H. A. Degenerative cardiovascular diseases in the Orient. *J. Chron. Dis.*, 8: 312, 1958.
13. Sen Gupta. Quoted by Vakil, R. J.[15]
14. Kutumbiah, P. Quoted by Vakil, R. J.[15]
15. Vakil, R. J. A study of hypertensive heart disease in India. *Indian Heart J.*, 2: 31, 1950.
16. Vakil, R. J. Statistical observations on cases of coronary thrombosis. *Indian Physician*, 2: 231, 1952.
17. Malhotra, R. P. Coronary heart disease. *Indian J. M. Sc.*, 5: 617, 1951.
18. Mathur, K. S. and Wahi, P. N. Asymptomatic myocardial Infarction. *Indian Heart J.*, 2: 130, 1950.
19. Mathur, K. S. Coronary occlusion syndrome in acute falciparum malaria. *Indian Heart J.*, 2: 130, 1950.
20. Mathur, K. S. Dietary fats, serum cholesterol and serum lipid phosphorus in different socioeconomic groups in Uttar Pradesh. *J. Indian M. A.*, 33: 303, 1959.
21. Mathur, K. S. Etiology—cor pulmonale. *Indian Heart J.*, 10: 1, 1958.
22. Bhatia, B. B. and Jain, S. C. Cor pulmonale. *Indian Heart J.*, 5: 117, 1953.

A Pharmacodynamic Approach to the Evaluation of Nitrites in the Treatment of Angina Pectoris*

IRVING HIRSHLEIFER, M.D., F.A.C.C.

Woodmere, New York

FEW drugs in any chemical class have so adequately withstood the test of time and achieved the widespread medical acceptance of the nitrites in the treatment of angina pectoris. Reliable pharmacologic studies in laboratory animals supported by decades of favorable clinical experience constitute impressive evidence of the remarkably consistent therapeutic benefits accomplished with octyl nitrite, amyl nitrite and particularly with glyceryl trinitrate (nitroglycerine). At present, no other agent will relieve angina pectoris associated with coronary insufficiency to the same extent and with as few therapeutic failures as nitroglycerine and, consequently, this drug is universally recognized as the yardstick against which are measured the newer long-acting vasodilator compounds as well as the older nitrites considered worthy of reappraisal.

For some time, the sublingual route has been the preferred pathway of administration for nitroglycerine and also for certain other vasodilating nitrites. Presumably, ingested material is poorly absorbed and hence less readily available for therapeutic action. The validity of this concept is, however, somewhat open to question in view of the admitted shortcomings and inadequacies of present day methods for evaluating vasodilating drugs. Even a superficial survey of the available literature discloses a variety of conflicting reports concerning the efficacy of different nitrite compounds which may be attributed to failures in experimental design, subjective differences in observation and to the lack of an objective means of detecting vascular dilatation following the administration of an appropriate drug. In addition, the substantial psychogenic factors in angina pectoris compound the usual difficulties encountered in determining the clinical value of any new substance. The challenge of objectivity can only be met by a dynamic approach to the evaluation of nitrites centered about the direct measurement of the circulation and the dilating effects of these compounds on a particular vascular bed. Early experience with a new and objective method for appraising vasodilating properties is presented in this communication.

EVALUATING THE VASODILATORS

Subjective Methods: Use of the symptom of pain to estimate coronary inadequacy and myocardial ischemia obviously introduces considerable error into the test procedure. Yet, in current practice, subjective methods of evaluation are widely employed to demonstrate the efficacy of various nitrite compounds. Subjective appraisals involve a measured amount of activity a patient can perform, preferably under standardized conditions, without inducing anginal pain.[1] A second method requires the patient to keep a diary noting work capacity, sense of well-being, episodes of discomfort and the quantity and frequency of nitroglycerine requirements.[2] The use of placebos or of a double blind experimental design may somewhat temper the purely subjective aspect of these studies but essentially the clinical acumen of the supervising physician determines the over-all result. It is not surprising, therefore, to encounter widely divergent reports as to the value of the available nitrite compounds and equivocal evidence

* From the Cardiac Clinic, Division I, Kings County Hospital Center, and the State University of New York, Downstate Medical Center, Brooklyn, New York.

of the suitability of one or another route of administration.

Electrocardiographic Methods: Presumably objective in nature, electrocardiographic methods leave much to be desired. A major difficulty is that only relatively few patients with angina are suited for this type of study. Even with selected patients, electrocardiographic changes are variable and it is frequently impossible to reproduce identical results on repeated tracings. Even at rest, the electrocardiogram may spontaneously show varying degrees of S-T depression on different days.[1] In addition, there is no constant relationship between the occurrence of electrocardiographic changes and the occurrence of cardiac pain.

It has been my experience in testing vasodilators that variations in the electrocardiogram may be completely independent of the coronary vasodilator administered or the therapeutic effect obtained.[3] Many patients exhibit no changes at all even after taking vasodilating medication for considerable periods of time. At best, from these measurements of the electrical potentials of heart muscle, an electrophysiologic estimate of the anoxic state of the myocardium is attempted and the state of dilatation of the coronary vessels indirectly inferred. This is indeed a roundabout way of measuring the degree of vasodilatation resulting from the administration of a nitrite.

Chemical Methods: Chemical methods, directed at the determination of blood nitrates,[4,5] no more demonstrate the therapeutic effectiveness of the coronary vasodilator tested than the pH of blood would demonstrate the value of an antacid for peptic ulcer.

Direct Measurement of Vasodilatation: The only truly objective and accurate procedure for evaluating the different nitrites in angina pectoris would require a direct measurement of their effect upon blood vessels. The desirable action of these compounds in angina is the dilatation of the coronary vessels through their influence on the unstriated vascular musculature.[6] While some believe that coronary dilatation is prolonged beyond the effect on other vascular beds,[7] it is generally agreed that all vascular beds are dilated and any difference that may exist is one of degree only. There is no vasodilator selectively specific for coronary vessels. Although utilization of the human coronary vessels to gauge the dilating action of the nitrites is not feasible, peripheral vessels are readily accessible and can be a practical source of information concerning the actual increase in blood flow attendant upon vasodilatation. The highly sensitive Winsor segmental pneumoplethysmograph, an instrument capable of accurately recording the pulse volume of a segment of a limb, appears to be ideally suited to the direct evaluation of vasodilating compounds.

The Segmental Plethysmograph

The segmental plethysmograph, developed by Winsor,[8] is a volume recorder indicating in cubic centimeters the volume changes which occur in a segment of a limb with each cardiac pulsation. The usual electrocardiograph may be employed to obtain tracings of these changes. Either an alternating or direct current recording apparatus may be attached to the plethysmograph. If an electrocardiograph is employed as a recording instrument the d.c. amplifier is entered through a manometer jack which is standard equipment on some. The same machine may be used as an alternating current recorder by plugging the segmental plethysmograph into the patient lead cable socket. In this way, sensitivity is increased fifty times.[9]

A cuff containing a bag, 8 by 40 cm., is placed on the limb to record volume changes. Regardless of the size of the area on which it is placed, the cuff is inflated with sufficient air to produce a pressure of 50 mm. Hg in the pneumatic system. An accurate standardization makes it possible to correct for differences in the volume of air in the pneumatic system when records are made from large and small parts of the body. The plethysmograph is highly sensitive and when set at standard sensitivity shows the presence of pulsations even when other oscillometers fail. By means of accurate standardization and gain control, factors which introduce errors into conventional oscillometry such as the volume of air in the cuff, tightness of the cuff, and aging of the rubber in the pneumatic system have largely been overcome. With this instrument, the following studies of the vasodilator properties of two clinically important nitrites were carried out.

Method of Study

Sixty subjects, both normal persons and those with coronary sclerosis and insufficiency, seen in private practice and at Kings County Hospital Center were subjected to plethysmographic examination and, in some instances, to comparative electrocardiographic study. The effects of the two vasodilators, nitroglycerine and erythrol tetranitrate,* following a single sublingual dose and a single oral dose were

* Supplied as Cardilate® through the courtesy of Dr. Stanley T. Bloomfield, Burroughs Wellcome & Co., Inc., Tuckahoe, New York.

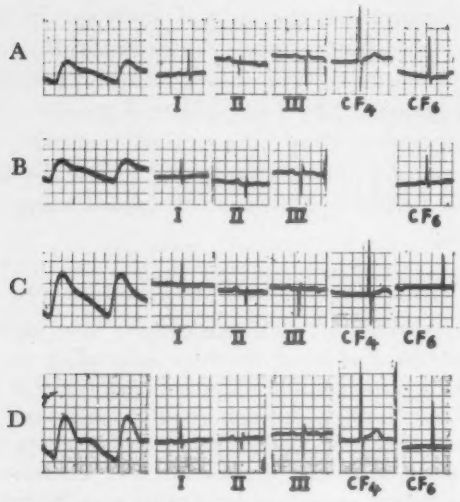


FIG. 1. Effects of administration of nitroglycerine and erythrol tetranitrate on plethysmogram and electrocardiogram in a fifty-two year old man with coronary disease. Blood pressure 120/80, blood cholesterol 208 mg. A, resting records. B, after two-step exercise test. C, after 0.3 mg. nitroglycerine sublingually. D, after two weeks of sublingual erythrol tetranitrate therapy, 15 mg. four times a day, three hours after last dose. Sensitivity of all plethysmographic tracings × 4.

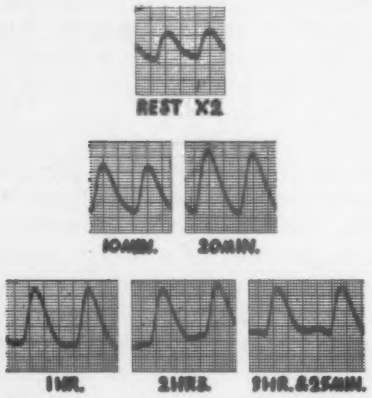


FIG. 2. Effect of erythrol tetranitrate therapy, 15 mg. administered sublingually, on plethysmogram. Recording sensitivity of all tracings × 2.

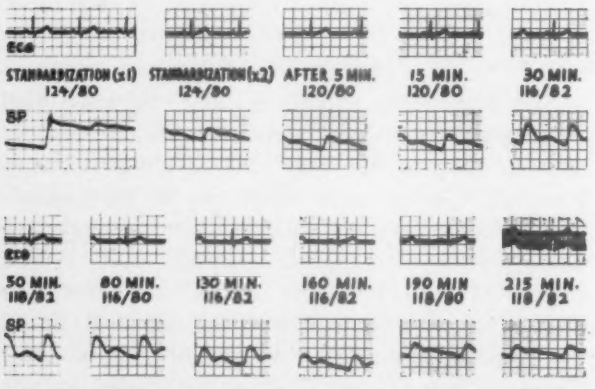


FIG. 3. Effect of erythrol tetranitrate therapy, 15 mg. administered orally. Recording sensitivity of all but first tracing × 2.

recorded under specific conditions described subsequently and illustrated in Figures 1 to 6. There were essentially two fundamental aspects to this investigation. The plethysmogram and the electrocardiogram were initially compared with regard to sensitivity to vascular changes induced by vasodilating drugs. Then, two prominent vasodilators were appraised for their clinical efficacy by sublingual and oral routes of administration. Representative findings are described in detail. In all cases, the pneumatic plethysmographic cuff was applied to the ankle.

RESULTS

Long-Term Effects of Erythrol Tetranitrate: In Figure 1 are presented comparative plethysmographic and electrocardiographic tracings obtained on a fifty-two year old man with coronary sclerosis and insufficiency. Recordings are shown with the patient at rest, after performance of the standardized Master's two-step exercise,[9] following a single administration of 0.3 mg. nitroglycerine sublingually, and finally after a two-week period during which erythrol tetranitrate was taken four times a day in doses of 15 mg. The final tracing was taken three hours after administration of the last tablet. Examination of the electrocardiograms and plethysmograms readily reveals that plethysmographic pulse waves are more satisfactory interpretations of changes induced by the vasodilator, nitroglycerine, than are electrocardiographic recordings. When, on another occasion, the same patient was given a single 15 mg. dose of erythrol tetranitrate, plethysmographic evaluation confirmed the prolonged action attributed to this drug.

Comparison of Sublingual and Ingested Erythrol Tetranitrate: The plethysmographic tracings

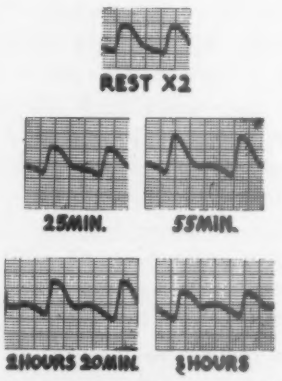


FIG. 4. Vasodilating effect of delayed absorption tablet of ingested nitroglycerine, 12 mg. in monostearate base.

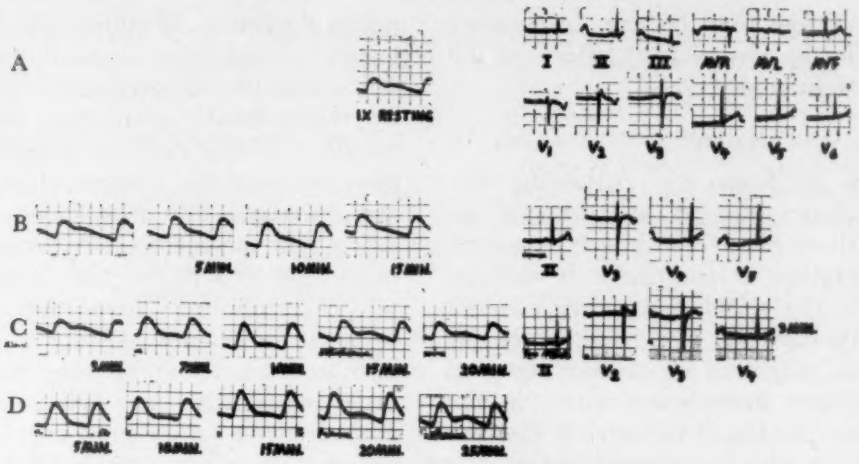


FIG. 5. Comparison of vasodilating effect of sublingual and ingested nitroglycerine in a normal twenty-three year old man. A, plethysmogram and electrocardiogram at rest. B, tracings after two-step exercise test. C, after sublingual administration of 0.3 mg. nitroglycerine. D, after oral ingestion of 0.3 mg. nitroglycerine. Sensitivity of all plethysmograms × 1.

in Figure 2 were obtained following sublingual administration of a single 15 mg. dose of erythrol tetranitrate. A significant vasodilating action was detectable as long as three hours and twenty-five minutes after the drug was given. When the same agent was swallowed in a single dose of 15 mg., onset of action was evident after five minutes, attained a peak after fifty minutes and was detectable up to three hours and thirty-five minutes after administration. These recordings are presented in Figure 3. It would appear, then, that the pattern of vasodilating action is essentially equivalent regardless of route of administration when an objective method of direct measurement is employed. Erythrol tetranitrate may be given orally as well as sublingually without impairment of therapeutic efficacy.

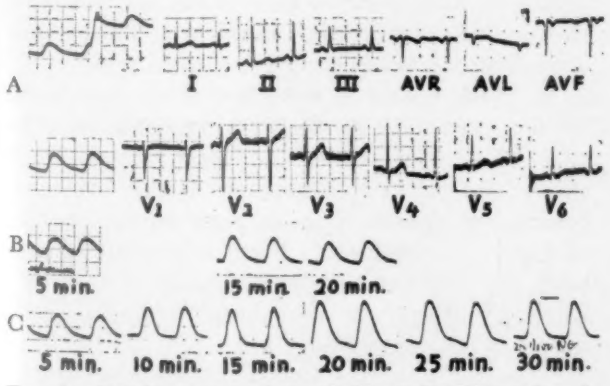


FIG. 6. Further comparison of effect of sublingual and ingested nitroglycerine. A, tracings at rest. Sensitivity of upper plethysmogram × 1, lower × 2. B, effect of sublingual administration of 0.3 mg. nitroglycerine. C, effect of 0.6 mg. ingested nitroglycerine.

Long-Acting Nitroglycerine: The recordings in Figure 4 demonstrate the delayed absorption of nitroglycerine carried in a monostearate base. By use of a monostearate carrier, the onset of vasodilating action of a single 1.2 mg. dose is delayed to fifty-five minutes after ingestion and the over-all duration of effect extends to two hours and twenty minutes. A long-acting form of nitroglycerine is prepared without much difficulty and is able to match or, at least, to approach the prolonged effects of some of the long-acting nitrite compounds.

Comparison of Sublingual and Ingested Nitroglycerine: In view of the finding that vasodilating effects induced by erythrol tetranitrate were virtually identical for oral and sublingual routes of administration, it was considered desirable to similarly appraise nitroglycerine, particularly since the sublingual route is proposed as the only truly effective one for this drug. Results are presented in Figure 5. On separate occasions a normal twenty-three year old man was given equal sublingual and oral doses of nitroglycerine after which comparative plethysmographic and electrocardiographic recordings were obtained with the subject at rest and after standard exercise. As before, a typical and similar picture of vasodilatation was observed, regardless of the route of administration. Objective evidence was obtained that nitroglycerine, like erythrol tetranitrate, exhibits essentially the same onset and duration of effect following ingestion as well as sublingual absorption. Confirmatory tracings are presented in Figure 6. Here, ingestion of 0.6

mg. of nitroglycerine may be seen to produce virtually double the vasodilating effects of 0.3 mg. absorbed sublingually.

Comment

Present day methods for evaluating the vasodilating nitrites possess in common inadequacies attributable to an oblique approach to the determination of drug-induced vascular changes and to the sizable subjective element in the interpretation of test results. Major discrepancies in judgment of efficacy reported by one or another investigator attest to the need for a direct means of measuring vascular changes occurring with the administration of a vasodilator. The Winsor segmental plethysmograph, by indicating volume changes with each cardiac pulsation, offers the first opportunity for a truly objective pharmacodynamic approach to the evaluation of nitrites. Early experience with this instrument proved that sensitivity to vascular changes was considerably greater than that of the electrocardiograph and that the plethysmogram uniformly yielded information directly reflecting drug action. Inconsistencies encountered in electrocardiographic studies of vasodilators were absent in plethysmographic recordings. Onset, peak and tapering-off of dilatation were clearly depicted so that the therapeutic usefulness of the test agent was readily gauged.

Employing the highly sensitive plethysmograph, comparative studies were conducted with nitroglycerine and with erythrol tetranitrate to determine whether sublingual administration was more advantageous than ingestion for eliciting a rapid response. When equal doses were given, both routes of administration were essentially equivalent in producing typical vasodilator activity patterns. It has been determined from observation of several scores of patients that the sublingual nitroglycerine tablet may take from thirty seconds to as long as eight minutes to disintegrate, with a mean of about one and a half minutes. The more extended disintegration time is particularly true for older age groups.

Since it is virtually impossible to refrain from swallowing several times during the period of disintegration, benefits of medication are somewhat derived from gastric as well as sublingual absorption. A universal experience is the dental aspirator placed in the mouth to remove collected salivary secretions and to prevent involuntary swallowing during dental manipulations. Without this device, swallowing would occur continuously as a result of the stimulus to increased salivation imparted by the presence of foreign materials in the mouth. It is a rational thought that a tablet placed under the tongue stimulates salivation and increases the urge to swallow both the saliva and the medication carried with it. In older age groups in particular, there is no practical clinical advantage to absorption from a sublingual position. The length of disintegration time sharply limits claims of rapid absorption and effect and differences attributed to sublingual over oral route of administration are probably insignificant. The oral route is certainly a more pleasant form of therapy.

Summary and Conclusions

1. Early experience with the Winsor segmental plethysmograph, an instrument highly sensitive to changes in pulse volume, demonstrated that a pharmacodynamic approach involving direct measurement of blood volume changes is an objective means of evaluating the vasodilating properties of nitrites.

2. Plethysmographic records offer direct evidence that with nitroglycerine or erythrol tetranitrate, sublingual or oral routes of administration are essentially equivalent in producing the desired therapeutic effect. Although it is now generally believed that the sublingual form is preferable for these vasodilator agents, objective appraisal indicates that onset, peak and tapering-off of induced dilatation is ostensibly the same following sublingual or gastric absorption of the drugs. From a subjective viewpoint, however, oral therapy is more desirable since a tablet held under the tongue is rather unpleasant and imparts a continuous sensation of a serious need for medication.

3. This report is intended as an indication of the potential in plethysmographic evaluation of the clinically important vasodilator drugs and to direct attention to this objective method of appraisal in an area largely devoid of such procedures. Further investigations with this instrument ideally suited to detecting dilating effects on peripheral vascular beds are currently underway.

References

1. Riseman, J. E. F., Altman, G. E. and Koretsky, S. Nitroglycerine and other nitrites in the treatment of angina pectoris. *Circulation*, 17: 22, 1958.

2. Fuller, H. L. and Kassel, L. E. Metamine (triethanolamine trinitrate biphosphate) in angina pectoris. *J. A. M. A.*, 159: 1708, 1955.
3. Hirshleifer, I. The effect on the coronary arteries of a new sustained action vasodilator. *Angiology*, 9: 31, 1958.
4. Feinblatt, T. M. and Ferguson, E. A. Timed disintegration capsules—a further study. *New England J. Med.*, 256: 331, 1957.
5. Berry, J. W. and Roach, T. C. An evaluation of blood nitrate levels. *Circulation*, 17: 1041, 1958.
6. Cushny, A. R., Edmunds, C. V. and Gunn, J. H. A Textbook of Pharmacology and Therapeutics. 11th ed., p. 629. Philadelphia, 1936. Lea and Febiger.
7. Goodman, L. S. and Gilman, A. The Pharmacological Basis of Therapeutics, 2nd ed., p. 730. New York, 1955. The Macmillan Co.
8. Winsor, T. The segmental plethysmograph. *Angiology*, 8: 87, 1957.
9. Master, A. M. The two-step exercise electrocardiogram. *Ann. Int. Med.*, 32: 842, 1950.

Plethysmographic Studies in Atherosclerosis Obliterans

ALFREDO BUZZI, M.D.

Buenos Aires, Argentina

ATHEROSCLEROSIS obliterans of the lower extremities constitutes almost 90 per cent of peripheral arterial disorders of organic nature. Its clinical manifestations, such as intermittent claudication, rest pain and absence of arterial pulses, are sufficiently distinctive to permit an accurate clinical diagnosis in the majority of cases.[1]

Although the correct diagnosis of the disease is simple it must be recognized that knowledge of the prognosis and natural history of the process is not entirely adequate. Concerning its most important complication, the development of gangrene, it can be postulated that tissue necrosis develops when the distal circulation is seriously impaired. Proximal arterial occlusion, such as aortic, iliac or common femoral, although producing intermittent claudication at the coxal, gluteal or sural regions, seldom produces gangrene of a limb. The proximal nature of the obstruction allows the growth of a collateral circulation, insuring an adequate distal blood flow during rest. It can be established, therefore, that gangrene usually begins at the distal regions, often precipitated by trauma or infection.

Current instrumental methods for the evaluation of these patients are oscillometry, ergometry, measurement of skin temperature, and angiography. Although the clinical value of digital plethysmography has been previously well established,[2–4] its use in clinical practice has not been generalized. This procedure is an objective method of evaluating the digital blood flow. Currently, the state of the distal circulation is estimated from the severity of trophic changes, such as atrophy of toe tips. When this has occurred the diagnosis is obvious, but treatment inefficient.

In the examination of patients with peripheral vascular disorders, we routinely determine the digital pulse volume by the plethysmographic method. It is the purpose of this paper to report a plethysmographic study in a series of patients with atherosclerosis obliterans of the lower limbs, and to emphasize the clinical value of the procedure in the objective estimation of the peripheral circulation.

MATERIAL AND METHODS

The studies were performed in a room with constant temperature showing variations of less than 1°C. Patients were examined after fifteen to thirty minutes of rest, and from three to six hours after lunch. Smoking and drinking of alcohol previous to the examination were prohibited. Both great toes were enclosed in rigid plethysmographic cups which were connected by means of plastic tubing to a volume recorder[5] sensitive to volume changes of 0.001 cc. The airtight seal of the cup was repeatedly checked during the examination. Measurement of digital volume was made by displacement of a colored solution. Symmetrical toes were examined, and in the case of amputation, the index finger was used. Once the tracings in the basal state were obtained, vasodilation by body heating or peripheral nerve block was produced. Recordings were made with a direct writing electrocardiograph at a paper speed of 25 mm. per second. Twenty-two patients with atherosclerosis obliterans of different severity were studied.

RESULTS

MORPHOLOGIC ABNORMALITIES

Morphologic changes of digital pulse volume in atherosclerosis obliterans are characteristic (Figs. 1 and 2), even when arterial stenosis is slight and does not reduce its amplitude. In patients with slightly advanced arterial disease, the peak is rounded and abnormally delayed. Dicrotic phenomena are absent. In normal subjects, crest time varies between 0.10 and 0.15 second, or 12 to 18 per cent of cycle length. In arterial occlusion, crest time is longer and proportional to the magnitude of

the obstruction, ranging between 0.16 and 0.35 second.

In patients with moderately advanced arterial disease, digital pulse volume is more flattened, and the peak barely discernible. Dicrotic wave and incisura are absent. In these conditions the curve has a sinusoidal aspect. In patients with severe arterial insufficiency, the digital plethysmogram is markedly flattened and the anacrotic segment almost horizontal.

QUANTITATIVE ABNORMALITIES

Reduction of toe pulse volume is not a constant finding in atherosclerosis obliterans. The proximal character of the occlusion, and in some cases its partial nature, as well as the development of a good collateral circulation, make possible the maintenance of an optimal digital blood flow. When the stenosed arterial segment is short and sufficient collateral arteries are present, as evidenced by arteriography or aortography, digital pulse volume may be normal. However, it will show the morphologic changes previously described. When arterial occlusion is more extensive, a diminished amplitude of toe pulse volume is present.

In normal persons, the amplitude of toe pulse volume varies between 2 and 5 cu. mm. per 5 cc. of part during rest, and between 4 and 11 cu. mm. per 5 cc. of part after induced vasodilatation. When arterial occlusion is extensive or the collateral circulation insufficient to bypass the obstruction, the plethysmographic values are reduced to between 1 to 3 cu. mm. per 5 cc. of part. If the popliteal, tibial, plantar or digital arteries are occluded, the reduction is greater and plethysmographic values are meager, between 0 and 1 cu. mm. per 5 cc. of part (Figs. 1, 2 and 3).

CORRELATION BETWEEN ANGIOGRAPHIC AND PLETHYSMOGRAPHIC FINDINGS

X-ray visualization of the stenotic arterial segment permits the estimation of morphologic details and the degree of poststenotic filling (Fig. 3). The magnitude of the collateral circulation is likewise established. The comparison of these radiologic data with plethysmographic findings indicates that an arterial stenosis of short length with an adequate collateral circulation can be accompanied by a digital plethysmogram of normal amplitude, even if the stenosis is localized at the aortic bifurcation or in the iliac arteries. There will be, however, typical morphologic abnormalities

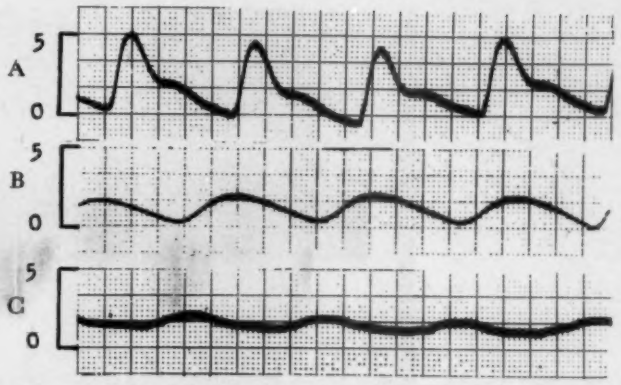


FIG. 1. A, digital pulse volume (big toe) of a normal subject. B, digital pulse volume of a patient with atherosclerosis obliterans, grade 2. C, digital pulse volume of a patient with atherosclerosis obliterans, grade 3. The morphological and quantitative differences can be appreciated. Amplitude scale at left indicates cu. mm. per 5 cc. of part.

of the pulse wave, particularly its sinusoidal aspect.

If the obstruction is extensive and the collateral circulation defective, the amplitude of the plethysmogram will be reduced and, of course, the abnormalities of the pulse contour will be evident. When the occlusive lesions diffusely involve the femoral artery or the arteries of the calf and foot, the digital plethysmogram is markedly flattened and its amplitude is about 1 cu. mm. per 5 cc. of part. In some patients with advanced arterial insufficiency it is impossible to obtain a digital pulsation (Fig. 3).

GRADING OF SEVERITY

According to our observations, and particularly as a result of the correlation between

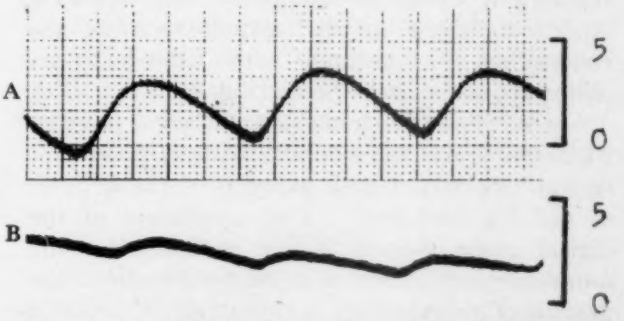


FIG. 2. A, digital pulse volume of a patient with minimal arterial stenosis. The amplitude of the curve is within normal limits but characteristic morphologic abnormalities are present. It corresponds to grade 1 severity. B, digital pulse volume of a patient with multiple occlusive lesions of the femoral artery and deficient collateral circulation, corresponding to grade 3. Scale same as Figure 1.

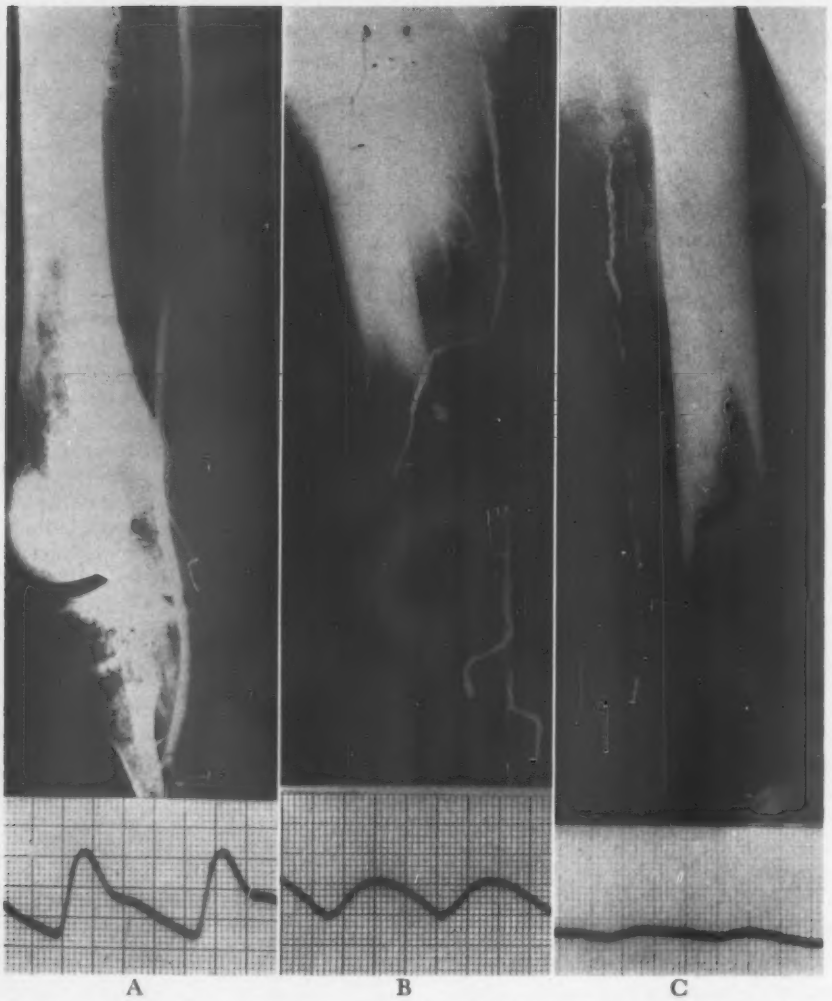


FIG. 3. A, arteriogram and corresponding digital plethysmogram of a subject without arterial disease. B, arteriogram and corresponding digital plethysmogram of a patient with atherosclerotic occlusion of the superficial femoral artery. C, arteriogram and corresponding digital plethysmogram of a patient with multiple occlusive lesions of the femoral artery.

arteriographic and plethysmographic data, we consider it useful to distinguish the following grades of severity of digital pulse volume abnormalities in patients with atherosclerosis obliterans of the lower limbs (Fig. 4).

Grade 1: In this group are included patients with short arterial stenosis, with a good collateral circulation and patency of the arteries of the leg and foot. The amplitude of the digital pulse volume is not reduced but the morphologic changes previously described are present (Fig. 2A).

Grade 2: This group includes patients with complete and relatively extensive arterial occlusion and moderately developed collateral circulation. The popliteal and tibial arteries are patent. In addition to morphologic abnormalities, the amplitude of the digital plethysmogram is reduced, the values oscillating between 1 and 3 cu. mm. per 5 cc. of part (Fig. 1B).

Grade 3: To this group belong patients with multiple and diffuse arterial lesions. Collateral circulation is deficient or non-existent and occlusion of the popliteal, tibial, plantar and digital arteries is common. Digital pulse volume is markedly reduced and its amplitude does not exceed 1 cu. mm. per 5 cc. of part. Occasionally, it is difficult to discern any pulse wave in the tracing (Figs. 1C and 2B).

COMMENTS

Recent progress in the direct surgical correction of arterial occlusion has evidenced the need of a first-hand knowledge of the functional circulatory reserve and the topography of the

obstructive lesions. The state of the popliteal, tibial, plantar and digital arteries is particularly important when a plastic graft operation is considered, for if they show occlusive lesions the result will be unsatisfactory. Although it can be expected that in the near future the successful restoration of the lumen of the tibial arteries will be achieved, it has not been feasible up to the present time. For this reason determination of the patency of the circulation of the leg and foot is of paramount importance in the preoperative selection of these patients. It is of interest that in those cases in which arteriography showed patency of the leg arteries, toe pulse volume had an almost normal or moderately reduced amplitude (grades 1 or 2 of our classification), depending on the severity of the femoral or iliac obstruction. The subjects showing occlusion of the popliteal artery or distal to it had, on the other hand, markedly reduced plethysmographic values, corresponding to grade 3 of our classification.

In addition to the usefulness of the plethysmographic procedure in the evaluation of the severity of the occlusion and patency of the distal circulation, information which is indispensable when arterial graft surgery is under consideration, it has an important prognostic significance. It must be reemphasized that necrotic lesions usually begin in the digital regions,[6] previously severely ischemic. The measurement of toe pulse volume can detect a permanent and severe reduction of blood flow in the initial period. When the digital ischemia fails to improve after medical or surgical treatment, the prognosis is serious as far as tissue vitality is concerned.

We have limited this presentation to digital pulse volume abnormalities, without including the determination of the rate of blood flow, because a direct correlation exists between both parameters.[7] The measurement of digital pulse volume is a simple test, and we believe the information it furnishes to be sufficiently valuable to recommend its routinue use in the clinical examination of patients with peripheral vascular disease.

Many classifications of the severity and topography of peripheral occlusive arterial disease are already available, and it would seem presumptuous, if not obsolete to offer a new one. That the present one does not take into account the localization of the obliterative lesion can be considered a disadvantage. We believe, however, that what matters in these cases is the severity of the occlusion and the extent of collateral circulation. An external iliac artery obstruction with good collaterals can be better tolerated than a lower femoral or popliteal occlusion. The degree of ischemia is particularly well reflected by the plethysmographic method; the latter is far more sensitive and quantitative but appreciably not more cumbersome technically than oscillometry.

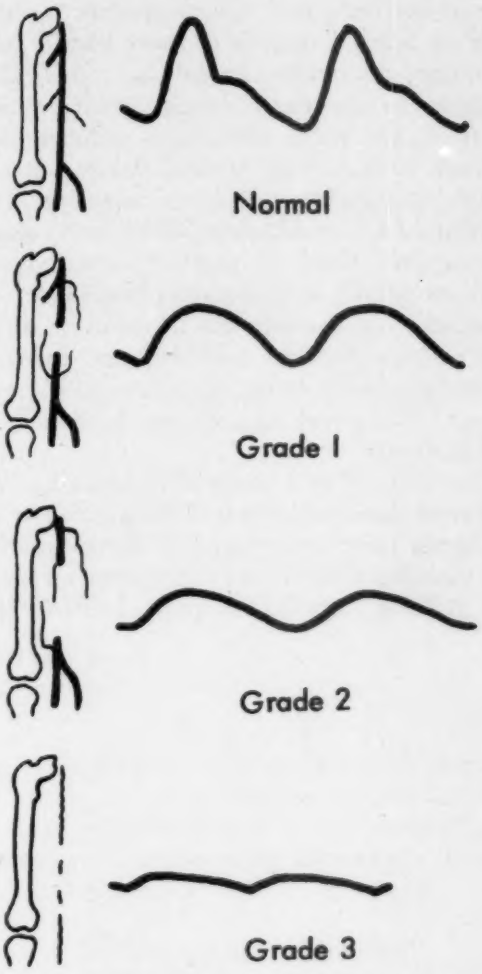


FIG. 4. Classification of the severity of occlusive arterial disease is outlined, showing the correlation of arteriographic and plethysmographic data.

SUMMARY

The abnormalities of digital pulse volume in a series of twenty-two patients with atherosclerosis obliterans of the lower limbs are reported. After a correlation between arteriographic and plethysmographic findings, three types of abnormalities are distinguished in the pulse volume contour: *Grade 1:* the peak is rounded, dicrotic phenomena are absent, and the curve has a sinusoidal aspect but its ampli-

tude is not reduced; it corresponds to patients with an arterial stenosis of short length and an adequate collateral circulation. *Grade 2:* in addition to the morphologic abnormalities of grade 1, toe pulse volume is reduced on an average to a half of normal values; it corresponds to patients with more extensive arterial occlusion and a moderately developed collateral circulation. *Grade 3:* marked flattening of the plethysmogram with meager amplitude values is present; it corresponds to multiple and diffuse occlusive lesions and frequent obstruction of the popliteal, tibial, plantar and digital arteries. Collateral circulation is deficient or non-existent.

The clinical and surgical significance of the observed abnormalities is discussed. The value of digital plethysmography in the estimation of the vascular reserve, the preoperative selection for grafting arterial surgery, control of the results of medical and surgical treatment, and prognosis of these patients is emphasized.

References

1. Buzzi, A. Diagnóstico y Tratamiento de las enfermedades arteriales periféricas. *Medic. Panam.*, 11: 297, 1958.
2. Goetz, R. H. Clinical plethysmography. *South African M. J.*, 22: 391, 422, 1948.
3. Winsor, T. Clinical plethysmography. *Angiology*, 4: 134, 149, 1953.
4. Kappert, A. Plethysmographische Untersuchungen in der angiologischen Praxis. *Praxis*, 40: 894, 1955.
5. Buzzi, A. Exploración de la circulación palmar y digital. *Medic. Panam.*, 12: 95, 1959.
6. Cranley, J. J., Buchanan, J. L., Simeone, F. A. and Linton, R. R. A critique of laboratory methods in peripheral vascular disease. *Surgery*, 31: 74, 1952.
7. Burton, A. C. The range and variability of the blood flow in human fingers and the vasomotor regulation of body temperature. *Am. J. Physiol.*, 127: 437, 1939.

Experimental Studies

Ventricular Fibrillation During and After Coronary Artery Occlusion

Incidence and Protection Afforded by Various Drugs*

SAM E. STEPHENSON, JR., M.D., RICHARD K. COLE, M.D., THOMAS F. PARRISH, M.D., FRANK M. BAUER, JR., M.D., IRA T. JOHNSON, JR., M.D., MORSE KOCHTITZKY, M.D., JAMES S. ANDERSON, JR., M.D., LESTER L. HIBBITT, M.D., JAMES E. MCCARTY, M.D., EDWIN R. YOUNG, M.D., JOHN R. WILSON, M.D., HENRY N. MEIERS, M.D., CLIFTON K. MEADOR, M.D., CON O. T. BALL *and* GEORGE R. MENEELY, M.D., F.A.C.C.

Nashville, Tennessee

VENTRICULAR fibrillation is a usually fatal episode in the natural history of coronary artery disease and during surgery, especially of the heart. The nature of this arrhythmia, which causes immediate cessation of the pumping action of the heart, precludes accurate estimate of its incidence[1] because it causes death in a matter of minutes. There are a few reports[1-8] of ventricular fibrillation in man recorded electrocardiographically, but in the brief time elapsing between the onset of this arrhythmia and death of the patient, there is seldom opportunity to confirm the diagnosis. It must, then, remain a suspicion rather than a conviction that many cases of sudden death in coronary artery disease and during anesthesia occur by this mechanism. Wiggers[9] clarified the relation of this lethal arrhythmia to myocardial infarction. No attempt has been made to review the entire literature of ventricular fibrillation. Since 1881[10] there have been numerous experimental investigations, much of the sort to be reported here. They have led to diverse conclusions. It is the purpose of this study to explore experimentally the incidence of ventricular fibrillation during and immediately after brief periods of temporary myocardial ischemia and to evaluate the protection afforded by certain drugs.

MATERIALS AND METHODS

1. CONTROL SERIES

The preparation was essentially that developed by Bayley, La Due and York.[11] Dogs were anesthetized intravenously with 26 to 30 mg. of pentobarbital sodium per kg. Small additional doses were administered when the eye wink reflex became active. The left side of the chest was opened utilizing positive pressure artificial respiration through a tracheal cannula. A small 0.5 by 0.5 cm. opening was made in the pericardium over the selected coronary artery. The vessel was isolated by blunt dissection with minimal trauma. A soft thread was slipped under the artery. Gentle traction on this ligature occluded the vessel. The artery alone was occluded. Electrocardiographic leads were taken from an electrode placed on the surface of the pericardium over the area irrigated by the occluded artery. The condition of the artery was determined by direct observa-

* From the Departments of Medicine, Surgery and Preventive Medicine and Public Health, Vanderbilt University School of Medicine, and the Research Laboratory, Thayer Veterans Administration Hospital, Nashville, Tennessee.

This work was supported in part by grants from the Division of Research Grants and Fellowships of the National Institutes of Health, Public Health Service, Ciba Pharmaceutical Products, Inc., Summit, New Jersey, the Eli Lilly Co., Indianapolis, Indiana and the National Drug Co., Philadelphia, Pennsylvania. Facilities employed were available through grants from the Commonwealth Fund, the United States Steel Foundation, Inc., and the United Givers Fund of Greater Chattanooga.

TABLE I

Incidence of Fatal Ventricular Fibrillation Observed in 330 Dogs Subjected to Occlusion of the Left Anterior Descending Coronary Artery for Thirty Minutes

Time of Ventricular Fibrillation	Total No. of Dogs	Incidence
During occlusion	330	91 (28% of total)
After release of occlusion	239	169 (71% of survivors)

tion and palpation during the experiment and by careful postmortem examination. The vessel reopened upon release of the ligature. In an experience with hundreds of similar preparations we have encountered thrombosis only once. The usual finding at the site of the occlusive ligature is a minimal wrinkling of the intima.

In 351 apparently normal street dogs the desired artery was successfully isolated without undue trauma. Two more dogs served as additional controls as will be described later. The control series was composed of three groups: groups 1 and 3 are part of the initial experiment, group 2 is a cumulation of the standardized initial and sequential experiments.

Group 1: In nineteen animals, branches of the left anterior descending artery were temporarily occluded. As had been the experience of others, it was found that ventricular fibrillation is more prone to occur the larger the artery occluded and the longer the duration of the occlusion. It therefore appeared desirable to examine the incidence of ventricular fibrillation under standardized conditions.

Group 2: Three hundred thirty dogs were subjected to occlusions intended to be of thirty minutes' duration, and in each of these the artery was isolated as high as possible, at an average distance of 10 mm. from the ostium in the sinus of Valsalva. The circumflex branch was not molested. One other branch, usually small, escaped in a few cases.

Group 3: Four animals served as controls; two underwent coronary artery dissections but traction was not made on the ligature; in the two others the chest was opened but the pericardium remained intact and vessels were not disturbed. No arrhythmias occurred in these control animals.

II. EVALUATION OF DRUG PROTECTION

A variety of drugs was tested to determine their protective action against the development of ventricular fibrillation during occlusion and following release of the ligature. Each drug tested was selected for some inherent property postulated as having an effect on cardiac arrhythmias. There were two series of experiments. The first series, group A, included 499 dogs, 208 treated and 291 standardized initial, sequential and concurrent controls. In the second series, group B, 116 dogs were treated and the standardized control series was increased to 330, a series total of 446 dogs. The work reported should be regarded only as an empiric approach to one aspect of the problem of ventricular fibrillation.

In addition to the previous experimental procedures, the effect of the drugs on the systemic blood pressure was tested. In seventy animals the left common carotid artery was isolated and cannulated while in eighty-five additional animals the left femoral artery was used. Blood pressure was recorded continuously from one or the other vessel with an ink writing mercury manometer and a kymograph. A 10 ml. solution of heparin was used as an anticoagulant in the recording apparatus only.

As a further experimental procedure, when ventricular fibrillation occurred, a Beck-Rand electrical defibrillator was employed for a period of five minutes in ninety animals. Cardiac massage was performed manually.

The drugs tested were administered in normal saline solution. In group B a *priming dose* was administered intravenously for an appropriate time prior to occlusion of the vessel and an appropriate *maintenance dose* was begun intravenously immediately following the priming dose. The dogs in group A were infused with the maintenance dose for five minutes prior to the occlusion of the coronary artery and throughout the occlusive period or until fibrillation occurred.

Control experiments were interspersed at random throughout both series. As the initial and sequential controls were remarkably similar to the concurrent controls they were included as controls for the series, i.e., the 291 controls for group A were increased to 330 controls for group B. In the control animals, only normal saline was administered, the same time intervals being observed. The volume of solutions administered was kept constant for the various drugs employed.

Quinidine: A freshly prepared solution of quinidine sulphate crystals in normal saline was prepared. The dose calculated by weight was 15 mg./kg. in a 1.5 mg./ml. solution. The drug was given intravenously over a ten-minute period starting ten minutes after occlusion of the artery and ending twenty minutes after occlusion, thus having peak action starting near the mid-point of the ischemic phase of the myocardium and extending over the period of release.

Procaine, Procaine Amide and Xylocaine: Dosages of procaine equivalent by weight to amounts used in human subjects were used. The dose administered was 4.6 mg./kg. in a 0.1 per cent solution.[12,13] This amount is significantly lower than the 15 mg./kg. reported by Burstein,[14] but a dose of this magnitude would not be comparable in our experiment to the other drugs tested. The procaine was also given over the mid-ten-minute period but was followed by a maintenance dose of 4.6 mg./kg./hr.

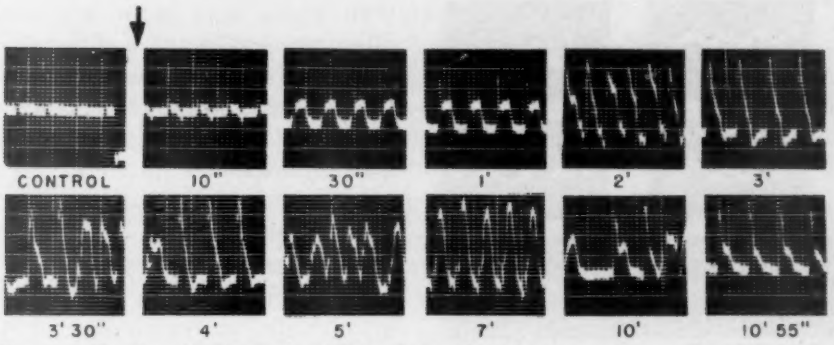


FIG. 1. Twelve clippings of serial tracings taken from an area rendered temporarily ischemic by closure of a branch of the anterior descending coronary artery by tension on a ligature slipped beneath it. The artery alone was occluded. The control tracing shows essentially flat T waves and the upper row of tracings following the onset of the occlusion marked by the arrow shows successive developing ischemia-injury patterns. By the end of two minutes a pattern suggestive of ventricular tachycardia had developed, in the three minute thirty-second clipping this had begun to become impure, and by five minutes there was frank ventricular fibrillation. However, by seven minutes the pattern had returned to ventricular tachycardia and by ten minutes and fifty-five seconds, the sinus rhythm with the ischemia-injury pattern was re-established. This is an example of transient ventricular fibrillation.

Procaine amide was used in the same dosage and concentration as procaine (4.6 mg./kg. in a 0.1 per cent solution).

Xylocaine (lidocaine HCl) was tested because of its similarity to procaine with the added advantage of prolonged effect. The dosage was the same as that of procaine, 4.6 mg./kg. in 0.1 per cent solution.

Su 1194 (Ciba), a ganglionic blocking agent, was used by the intravenous route with a dose of 3 mg./kg. over the mid-ten-minute period, followed by a maintenance dose of 3 mg./kg./hr.

Pendiomide (Ciba 9295), a compound with similar ganglion-blockading effect as Su 1194, was used in the same dosage.

Trasentine®: Trasentine is a synthetic spasmolytic substitute for atropine which is an effective relaxant of smooth muscle but does not inhibit vagal stimulation of the heart. This drug is an ester of alkaminoethanol, one of the byproducts of procaine metabolism, and was reported by McCawley and White[15] to exhibit the same effect as procaine, milligram for milligram, in response to ventricular arrhythmia induced by drugs. Trasentine was administered in a freshly made solution of 10 mg./kg. over the mid-ten-minute period followed by a maintenance dose of 10 mg./kg./hr.

Paveril® Phosphate: This drug has been recommended as a potent coronary dilator.[16] Thirty dogs were tested. A priming dose of 5 mg./kg. given over a ten-minute period was followed by a maintenance dose of 5 mg./kg./hr. administered by a continuous drip.

Adenosine Triphosphate: This compound was tested in fourteen dogs since it is known to have a marked vasodilator effect and because of its energy-rich phosphate reserve for myocardial metabolism.[17] Little is known, however, of its effect on a heart rendered susceptible to ventricular arrhythmia. The priming dose was the same as that for Paveril.

Regitine®: Many investigators have confirmed the fact that Adrenalin® could precipitate episodes of ventricular arrhythmia in hearts sensitized in various fashions (chloroform, anoxia, caffeine, etc.). It seemed important to determine whether anti-adrenergic drugs could protect against ventricular fibrillation induced by temporary coronary artery occlusion.[18] Regitine, selected for its potent anti-adrenergic effect,[19] was administered to twenty-nine animals. The priming dose was given as 0.5 mg./kg. over a five-minute period followed by a maintenance dose of 2 mg./kg./hr. over the period of occlusion. The maintenance dose was continued at the same rate until the experiment was terminated.

Apresoline®: Previous studies have shown some promise of protection from autonomic blocking agents.[20] Thirty dogs were subjected to experimental evaluation using Apresoline. A priming dose of 0.5 mg./kg. given over a ten-minute period was followed by a maintenance dose of 1 mg./kg./hr. begun immediately following the priming dose.

Priscoline®: Priscoline was evaluated because of its sympatholytic and adrenalytic activity and also for its vasodilator action on the intrinsic musculature of the vessels.[21] Thirteen animals were in this series. A priming dose of 3 mg./kg. was given over a ten-minute period followed immediately by a maintenance dose of 10 mg./kg./hr. infused over the total period of occlusion.

RESULTS

CONTROL SERIES

The first group of nineteen control experiments was not sufficiently consistent in duration

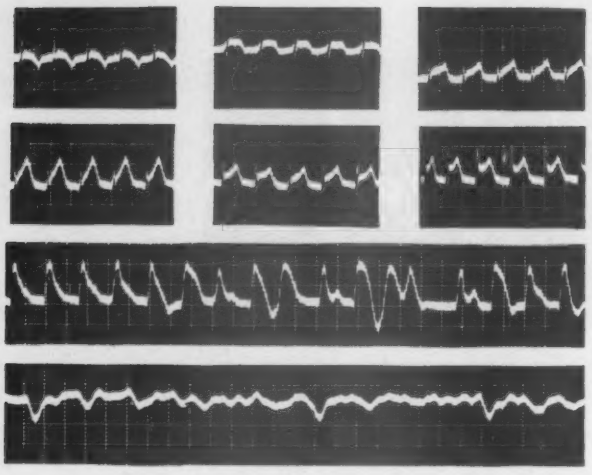


FIG. 2. The upper six clippings show the developing ischemia-injury pattern in an area rendered ischemic by closure of the irrigating artery. The *upper long strip* shows a rhythm suggestive of ventricular tachycardia becoming impure. As the tracing continued (*lower long strip*), this impurity became more pronounced to the final stage, frank ventricular fibrillation.

of ischemia or in size of vessel occluded to warrant detailed description. Five cases of ventricular fibrillation occurred in these nineteen experiments.

The relevant data concerning the 330 "standardized" experiments (Table I) may be summarized thus: 28 per cent of the 330 dogs developed ventricular fibrillation during thirty minutes of occlusion of the anterior descending coronary artery. Of the 239 dogs who survived this thirty-minute period, 71 per cent developed ventricular fibrillation upon release of the occlusion. This is a highly significant difference ($P<0.001$).

Transient ventricular fibrillation was seen occasionally in the "standardized" experiments. In one of the preliminary studies a brief period of transient ventricular fibrillation was recorded electrocardiographically (Fig. 1, five minutes).

Figure 2 illustrates the mechanism of the development of ventricular fibrillation as observed in our animals. The first six tracings show the developing ischemia injury pattern during the earlier period of the occlusion. The upper of the two long strips illustrates ventricular tachycardia becoming impure and the lower of the two long tracings shows the final degeneration of rhythmicity.

There was a critical interval of three minutes between twelve and fifteen minutes after initiation of the occlusion, which was characterized by a relatively high incidence of arrhythmia. In earlier experiments, brief periods of arrhythmia were prone to occur, but not at any characteristic time, a difference we ascribe to the variability of experimental conditions in the first nineteen studies. The arrhythmias characteristically seen during ischemia in the standardized experiments were: single or multiple extrasystoles, coupled rhythms, runs of ventricular tachycardia and in seventy-six dogs, fatal ventricular fibrillation. Frequently, ventricular fibrillation was heralded by extrasystoles and/or ventricular tachycardia.

DRUG-TREATED ANIMALS (GROUP A)

The results may be seen in Table II (group A). Originally, fibrillation on release of the occluded artery was regarded as the prime "test of efficacy" of the drug in question but as data accumulated, protection afforded by drugs against fibrillation during ischemia became evident. In retrospect, protection during the ischemic period might have been improved had a priming dose of the drug been administered prior to the actual occlusion of the artery and then supplemented with a maintenance dose throughout the period of occlusion and release.

Quinidine Sulphate: In the dosage of quinidine employed, which may not be optimal, a significant reduction in the incidence of the arrhythmia was demonstrated. A 7 per cent incidence of fibrillation during occlusion and 47 per cent following release of the anterior descending branch of the left coronary artery was statistically highly significant (Table II, group A).

Procaine: Table II shows the striking reduction in fibrillation during occlusion of the artery but no change in the incidence of fibrillation on release. It was also noted in some animals that speeding up the maintenance infusion had no effect on the fibrillation and we were not able to revert a fibrillating ventricle to normal rhythm with procaine.

Procaine Amide: Similar results for protection during occlusion were found with this drug. The incidence of fibrillation was reduced from 26 to 11 per cent. However, procaine amide differed from procaine in that the reduction in the incidence of fibrillation following release of the artery from 71 to 58 per cent gave a strong suggestion ($P<0.1$) that it might be of value in reducing delayed arrhythmias. Although these data are encouraging, the protection against ventricular arrythmia is not as great as its value against auricular fibrillation as reported by Schlachman and associates.[22]

Using procaine amide we were able to record

TABLE II

Influence of Various Drugs on the Incidence of Ventricular Fibrillation Following Temporary Occlusion of a Major Coronary Artery

Experiment	No. of Dogs	Fibrillating with Occlusion		No. Surviving	Fibrillating on Release	
		No.	Per Cent		No.	Per Cent
Group A: 499 Dogs						
Control	291	76	26	215	153	71
Quinidine	41	3	7*	38	18	47
Procaine	19	0	0*	19	14	74*
Procaine amide	70	8	11*	62	36	58
Xylocaine	15	5	33	10	5	50
Su-1194	16	3	19	13	10	77
Pendiomide	31	4	13	27	14	52†
Trasentine	16	3	19	13	9	69
Group B: 446 Dogs						
Control	330	91	28	239	169	71
Paveril phosphate	30	15	50†	15	9	60
Adenosine triphosphate	14	6	43	8	4	50
Regitine	29	10	34	19	7	37†
Apresoline	30	5	17	25	11	44†
Priscoline	13	10	77†	3	1	33

* Highly significant protection $P < 0.02$.
† Significant difference $P < 0.05$.

two episodes of ventricular fibrillation which cleared spontaneously. This was the only drug tested that gave spontaneous reversion to a normal sinus rhythm under the conditions of the experiment.

Xylocaine (Lidocaine): Xylocaine differed from procaine and procaine amide in showing no apparent protection during occlusion of the artery (Table II, group A). However, it was similar to procaine amide in reducing the incidence of fibrillation on release from 71 to 50 per cent.

Su 1194 (Ciba): The results in Table II, (group A) show that there was no beneficial effect on the incidence of ventricular fibrillation during occlusion or after release.

Pendiomide: The incidence of fibrillation on release of the artery was reduced by approximately 19 per cent, which is a significant reduction (Table II, group A).

Trasentine: There were observed no significant effects in contrast to the excellent results reported.[23]

DRUG-TREATED ANIMALS (GROUP B)

Paveril: Ventricular fibrillation during occlusion developed in 50 per cent of the animals. Ventricular fibrillation on release of the occlusion developed in 60 per cent of the surviving dogs (Table II, group B). In comparison with control data, it appears, therefore, that under the conditions of this experimental procedure Paveril phosphate does not offer any degree of protection against the development of cardiac arrhythmia following periods of coronary occlusion.

Adenosine Triphosphate: Ventricular fibrillation during occlusion of the coronary artery developed in six (43 per cent) of the 14 animals. Of the surviving dogs, ventricular fibrillation on release developed in 50 per cent (Table II, group B). Therefore, there was no significant protection demonstrated for this drug against the development of fibrillation.

Regitine: Ten (34 per cent) of the twenty-nine dogs tested fibrillated during the "occluded" period. In seven (37 per cent) of the surviving animals ventricular fibrillation on release of the occlusion developed. This drug showed significant protection ($P<0.01$) on release of the artery but no increased protection over the period of occlusion. The over-all

TABLE III
Defibrillation after Experimentally Induced Ventricular Fibrillation in Ninety Dogs

Group	No. of Dogs in Whom Defibrillation Attempted for Five-Minute Period	Successful Defibrillation			
		Effective Blood Pressure Maintained		Effective Blood Pressure Not Maintained	
		No.	Per Cent	No.	Per Cent
Control	15	14	93	0	0
Paveril phosphate	24	21	88	2	8
Adenosine triphosphate	10	10	100	0	0
Regitine	14	10	71	4	29
Apresoline	16	5	31	10	62
Priscoline	11	7	64	4	36

incidence of ventricular fibrillation with Regitine, however, is significantly lower than in the control series (Tables II, group B and III).

Apresoline: In five (17 per cent) of the thirty dogs tested ventricular fibrillation developed during the period of occlusion (Table II, group B). This showed a marked improvement over the control series in reduction of the incidence of ventricular fibrillation during the occluded or anoxic phase of the experiment. Ventricular fibrillation on release of the occlusion developed in eleven (44 per cent) of the twenty-five surviving animals. This also showed significant protection during the latter phase of the experiment. Therefore, Apresoline significantly reduced the incidence of ventricular fibrillation in the over-all series, both in the anoxic and reperfusion phases of the experiment.

Priscoline: Ventricular fibrillation during the "occluded" period developed in ten (77 per cent) of the thirteen dogs. In one of the three remaining dogs ventricular fibrillation developed on release of the occlusion. This marked increase in ventricular arrhythmia during the period of occlusion seems to preclude any protective effect with Priscoline (Table II, group B).

Blood Pressure: An analysis of systemic arterial pressure studies was attempted since this should give an indication of coronary perfusion. No correlation could be demonstrated between changes in arterial pressure and the subsequent development of ventricular fibrillation. As would be expected, the onset of the arrhythmia was followed immediately by peripheral vascular collapse. The only consistent finding was a significant elevation of arterial pressure in the dogs receiving Priscoline and a paradoxical increase in the incidence or ventricular fibrillation.

Defibrillation: Seventy-five per cent of the dogs (ninety in whom defibrillation was attempted) were successfully restored to normal sinus rhythm. Of these sixty-seven animals, twenty (29 per cent) did not adequately maintain systemic arterial pressure. The variations in the individual groups are shown in Table III. It is of interest that Apresoline, the drug that demonstrated a highly significant protection for the heart against the development of ventricular fibrillation, also rendered the heart more difficult to resuscitate.

Comments

The conditions for development of ventricular fibrillation have been considered to be threefold: (1) a sufficiently large available circus pathway; (2) the existence of regions of variable recovery of excitability or local block; and (3) an adequate stimulus occurring at an appropriate time in the cardiac cycle. In relation to the first requirement, the ventricle of man is considered to be a more favorable site for the perpetuation of ventricular fibrillation than that of the dog because it is larger and thus offers more and longer circus pathways, as Garrey [24] first pointed out. The fundamental alterations of myocardial metabolism which promptly follow anoxemia or ischemia may supply the second condition of local regions of impaired conduction, if not frank block. The third condition may be met by spontaneous contractions originating in abnormal ventricular foci as they are a very common sequel to myocardial ischemia.

Blumgart[25] has summarized the factors in-

fluencing ventricular fibrillation in experimental myocardial ischemia thus: (1) size of artery occluded; (2) region of the heart supplied by the artery occluded; (3) duration of the occlusion; (4) nature of the anesthetic agent; (5) activity of the autonomic nervous system; and (6) changes consequent to re-establishment of the circulation. In 1896 Porter[26] stated that the incidence of ventricular fibrillation is in proportion to the size of the artery ligated. There is a question as to whether the second of the factors listed by Blumgart may not indeed be synonymous with the first. However, it seems reasonable to suppose that different parts of the ventricle have different susceptibilities to fibrillation, in view of known gradients of other physiologic properties. The importance of the duration of occlusion has been impressed upon all who have investigated ventricular fibrillation. The effects of anesthetics on the heart are of extreme interest. Levy[27] found that "a touch of the finger or an instrument, stimulation of a sensory nerve, section of the vagi, or their paralysis by atropine . . . " might provoke ventricular fibrillation in cats anesthetized with chloroform. A similar "readiness to fibrillate" is induced by local ischemia.[28] The behavior of myocardial capillaries injured by ischemia[29] should be added to the changes subsequent to re-establishment of circulation cited by Blumgart.

Incidence of Experimental Ventricular Fibrillation: From the experience of others, we have attempted to assess the incidence of ventricular fibrillation in dogs subjected to experimental occlusion of the anterior descending coronary artery. The table prepared by Burchell[30] was of material assistance. In 1881 Cohnheim and Von Schulthess-Rechberg[10] reported that ligation of the anterior descending coronary artery "always" resulted eventually in ventricular fibrillation. Moreover, early release of temporary ligations of the main anterior descending coronary artery "always" resulted eventually in ventricular fibrillation. Moreover, early release of temporary ligations of the main anterior descending artery initiated ventricular fibrillation within a few seconds in their dogs. Half of Porter's[31] eight dogs underwent ventricular fibrillation within 2.25 to 5.5 minutes after ligature of this artery. On the other hand, all eight dogs of Hirsch and Spalteholz[32] survived this operation, recovering completely without disability. Miller and Matthews[33] also found no immediate mortality in their series of ligations of the anterior descending coronary artery. (They also ligated the vein.) In 1918 Smith[34] performed similar experiments on eleven dogs with an immediate mortality of one dog from ventricular fibrillation. Coelho and Rocheta[35] described ventricular fibrillation early after ligation of a coronary artery as occurring "quelquefois." Clerc and his associates[36] investigated five dogs in this respect and found "ligation of the anterior descending coronary artery permits sometimes a survival of more than an hour." Feil et al.[37] found that 54 per cent of twenty-six dogs died of ventricular fibrillation during the first hour following ligation of the artery under discussion. In 1933 Parade[38] investigated nine dogs and "most" survived.

In the same year Leriche and Fontaine[28] reported their important observations of a "large number" of dogs. In their earlier experiences, ligation of the anterior descending coronary artery caused death in the majority of animals. Later, when their "experimental experience had become sufficiently large . . . fibrillation occurred only exceptionally." This interesting difference between their earlier and later series was explained thus: "But, the ligation being made and the heart not fibrillating, if one causes an excitation whether of the heart, of its arteries, of its nerves, or of the thoracic wall, fibrillation promptly occurs." They concluded "that fibrillation is the result of a reflex which superimposes its action of inequilibrium on the preparatory influence of ischemia." While some criticism may be leveled at the vagueness of the expression "inequilibrium" (desequilibre), it is, nevertheless, evident that sufficient attention has not been paid to the fundamental observation made by these authors on the ischemic preparation for ventricular fibrillation. The relation of these comments to those of Levy[27] concerning chloroform and the heart is obvious.

Cox and Robertson[39] found that two of their ten dogs died as a result of ventricular fibrillation "immediately." Harris and Hussey[40] lost 30 per cent due to "immediate" fibrillation, but they also tied the vein. Gross and Calef[41] gave no figures, but described ventricular fibrillation as occurring with great frequency. Blumgart et al.[42] lost one of four dogs through ventricular fibrillation upon reopening of a branch of the left anterior descending coronary artery following occlusions lasting from twenty to forty minutes. Yodice[43] lost three of eighteen dogs "within minutes" after ligation and Schauer et al.[44] lost 29 per cent of their dogs "immediately."

The variety of results in the above experiments ranges from inevitable fibrillation to a zero incidence of the same. The observations of Leriche and Fontaine[28] suggest that the variation from one author to another may be technical.

In the light of the reported variability of incidence of experimentally induced ventricular fibrillation, it is interesting to note that the incidence in the procedure reported in this paper has held remarkably constant. Based on the first ten dogs, it was 75 per cent upon release of the artery. By the time the series totaled ninety-three the incidence was 68 per cent. When the control series totaled 291 dogs and, finally, 330 dogs, the incidence was 71 per cent.

The essential effect of ischemia is to set the stage for ventricular fibrillation. The effect of the re-entry of blood is to precipitate an event for which ischemia has already laid the groundwork. It then becomes very difficult to evaluate ischemia versus reopening of the artery in relationship to the production of ventricular fibrillation. Nevertheless, it is evident that, under the conditions of our experiments, the hazard of fibrillation during ischemia is less than the hazard upon re-entry of blood to the ischemic area.

Effect of Various Drugs: While the incidence of ventricular fibrillation in coronary disease is unknown, the evidence suggests it may be a frequent disaster. The experimental procedure described offers a method to test various agents in ventricular fibrillation induced by noxious stimuli similar to those which may precipitate the arrhythmia in coronary artery disease in man.

Of the various drugs tested, quinidine was found to exert the greatest protective action during and following release of the coronary ligature. Quinidine is perhaps the oldest of the drugs tested and enjoys the best reputation for preventing and combating ventricular fibrillation.[45,46] Although the drug has many modes of action, the primary attribute in controlling arrhythmias according to Gold[47] is the ability to increase the refractory period of the various cardiac structures. Favorable results have been reported[47–50] on quinidine in the treatment of ventricular tachycardia and in preventing the progression of this arrhythmia into a fatal episode of fibrillation.

The fear of toxic reaction to quinidine has presented a problem. We observed no severe toxic manifestation in doses of 15 mg./kg. if the quinidine was administered slowly. If the rate of infusion was too rapid, however, an increased incidence of ventricular premature contractions was noted. In other experiments in our laboratory, doses of 30 to 40 mg./kg. have been administered without difficulty.[51] Rakov[52] has reported evidence of ventricular fibrillation following the intravenous administration of quinidine but this has not been observed by us.

The reduction of cardiac irritability by procaine was demonstrated in 1908 when Kochmann and Daels[53] first reported that topically applied procaine reduced cardiac irritability. This was confirmed by many authors and in 1931 Hermann and Jourdan[54] stated that intravenously administered procaine protected dogs from ventricular fibrillation produced by epinephrine. The work of Shen and Simon[55] later confirmed this. Many writers have pointed out the beneficial effect of procaine in protecting the heart against arrhythmia with a pacemaker derangement. The effectiveness in ventricular fibrillation has been debatable. Burstein et al.[56] have shown that in epinephrine-cyclopropane fibrillation in dogs a normal rhythm may follow intracardiac injection of procaine, but Stutzman and associates[57] were unable to confirm this finding.

Procaine, in addition to its quinidine-like effect on prolonging the refractory period of the cardiac cycle, reduces the excitability of the cardiac extrinsic nerves and slows conduction in the bundle of His.

The metabolism of procaine is more rapid than that of quinidine. For this reason the procedure was by necessity varied and, in addition to a priming dose, a maintenance dose was also employed in the experiments. Although procaine reduced the incidence of fibrillation during coronary occlusion, it did not protect against fibrillation following release of the occlusion and never reverted the fibrillation to normal. These results are in agreement with those of Harris et al.[58] who found procaine to be of little value in protecting the heart from fatal ventricular fibrillation following myocardial infarction.

It has been proved experimentally that the metabolites of procaine were also effective in high concentration against ventricular arrhythmia. Employed experimentally against cyclopropane-epinephrine arrhythmias, procaine amide was found effective in thirteen of fifteen animals with ventricular tachycardia.[59] The literature now has numerous reports of the efficacy

of procaine amide in the treatment of auricular fibrillation and flutter and ventricular tachycardia and fibrillation. Schaffer[60] reported that there was no preferential effect of Pronestyl® on the ventricle when given orally and that it is only 25 per cent as effective as quinidine. Harris et al.[58] reported that procaine amide is very effective in reducing the frequency of severe ectopic tachycardias at safe, low levels of the drug.

Our experimental findings indicated that procaine amide offered excellent protection against fibrillation during coronary occlusion but on release the beneficial effect was only suggestive. However, it is more effective in this respect than procaine. It is more useful than procaine due to its ease of administration, i.e., intravenous, intramuscular or oral, and its prolonged action. Bellet and associates[61] have reported that intramuscular use is as effective as other modes of administration with approximately 50 to 60 per cent of the drug being excreted unchanged in the urine, since the drug is not affected by procaine esterase.

Summary

The incidence of ventricular fibrillation during and after temporary experimental occlusion of the left anterior descending coronary artery or its branches was studied in 351 dogs. A standardized procedure of thirty-minute temporary occlusion of this artery was employed in 330.

There is usually a critical period after twelve and up to fifteen minutes of ischemia which is characterized by a tendency to arrhythmia: extrasystoles, singly or in runs, ventricular tachycardia, or both extrasystoles and tachycardia if not a fatal ventricular fibrillation. Several instances of transient ventricular fibrillation were observed.

Of 239 animals surviving thirty minutes of occlusion, 71 per cent developed ventricular fibrillation immediately *after* release of the artery, while only 28 per cent of 330 animals developed fibrillation *during* the occlusion.

The re-establishment of blood flow to an area of the myocardium made ischemic for thirty minutes by occlusion of the anterior descending coronary artery is more likely to precipitate ventricular fibrillation than is the period of ischemia itself.

Various drugs were evaluated in 324 dogs. Quinidine was the most effective drug in affording protection from ventricular arrhythmia during (7 per cent) and following (47 per cent) occlusion. Procaine, procaine amide and Apresoline offered good protection during the ischemic period. Apresoline and Regitine also reduced the incidence (44 and 37 per cent) of ventricular fibrillation upon reopening the ligature. Of the other drugs tested, only one, pendiomide, showed significant protection (52 per cent incidence).

Systemic arterial pressures did not predict the onset of ventricular arrhythmia. Electrical countershock accomplished cardiac resuscitation in 75 per cent of the fibrillating dogs. From these experiments, quinidine appears to be the drug of choice in the prophylaxis of fatal ventricular arrhythmias.

Acknowledgments

The authors wish to express their appreciation of the late Dr. Walter E. Garrey's advice and assistance and to Dr. Benjamin Robbins and Dr. H. B. Burchell for reviewing the manuscript.

References

1. Woods, R. M. and Barnes, A. R. Factors influencing immediate mortality after acute coronary occlusion. *Am. Heart J.*, 24: 4, 1942.
2. Zimdahl, W. T. and Fulton, F. T. Transient ventricular fibrillation: Report of a case with spontaneous recovery. *Am. Heart J.*, 32: 117, 1946.
3. Borg, J. F. Observations on the occurrence and prevention of sudden death. *Tr. Am. Therap. Soc.*, 39: 115, 1939.
4. Thompson, T. Ventricular fibrillation causing sudden death of a patient with disease of the left coronary artery. *J. A. M. A.*, 116: 2583, 1941.
5. Sigler, L. H. Case of ventricular fibrillation following acute coronary occlusion. *New York J. Med.*, 40: 218, 1940.
6. Smith, F. J. Ventricular fibrillation as a cause of sudden death in coronary artery thrombosis. *Am. Heart J.*, 17: 735, 1939.
7. Miller, H. Ventricular fibrillation as mechanism of sudden death in patients with coronary occlusion. *New England J. Med.*, 221: 564, 1939.
8. Hamilton, R. L. and Robertson, H. Electrocardiographic studies of the dying heart in angina pectoris. *Canad. M. A. J.*, 29: 122, 1933.
9. Wiggers, C. J. Mechanism and nature of ventricular fibrillation. *Am. Heart J.*, 20: 399, 1940.
10. Cohnheim, J. and Von Schulthess-Rechberg, A. Ueber die Folgen der Kranzarterienverschleissung fur das Herz. *Virchows Arch. path. Anat.*, 85: 503, 1881.
11. Bayley, R. H., LaDue, J. S. and York, D. J. Electrocardiographic changes (local ventricular ischemia and injury) produced in the dog by temporary occlusion of a coronary artery, showing a new stage in the evolution of myocardial infarction. *Am. Heart J.*, 27: 164, 1944.
12. Abbott, O. A. Personal communication, 1948.

13. Robbins, B. H. Personal communication, 1948.
14. Burstein, C. L. The utility of intravenous procaine in the anesthetic management of cardiac disturbances. *Anesthesiology*, 10: 133, 1949.
15. McCawley, E. L. and White, J. M. Protective agents for cyclopropane. Epinephrine induced cardiac arrhythmias. *Am. J. Med.*, 8: 526, 1950.
16. Henderson, F. G., Shipley, R. E. and Chen, K. K. Pharmacological studies of 6, 7-dimethoxy-1 - (4′ - ethoxy - 3′ - methoxybenzyl) - 3 - methyl-isoquinoline. *J. Am. Pharm. A.*, 40: 207, 1951.
17. Drury, A. N. and Szent-Györgi, A. Physiological activity of adenine compounds with especial reference to their action on the mammalian heart. *J. Physiol.*, 68: 213, 1929.
18. Levy, A. G. The genesis of ventricular extrasystoles under chloroform with special reference to consecutive ventricular fibrillation. *Heart*, 5: 299, 1914.
19. Freis, E. D., MacKay, J. C. and Oliver, W. F. The effect of "sympatholytic" drugs on the cardiovascular responses to epinephrine and norepinephrine in man. *Circulation*, 3: 254, 1951.
20. Moyer, J. H., Handley, C. A. and Huggins, R. A. Some pharmaco-dynamic effects of 1-hydrazinophthalazine (C 5968) with particular reference to renal function and cardiovascular response. *J. Pharmacol. & Exper. Therap.*, 103: 368, 1951.
21. Chess, D. and Yonkman, F. F. Adrenolytic and sympatholytic actions of priscol. *Proc. Soc. Exper. Biol. & Med.*, 61: 127, 1946.
22. Schlachman, M., Benjamin, J. W. and Terranova, R. The termination of auricular fibrillation in dogs with procaine amide hydrochloride. *Am. Heart J.*, 42: 284, 1951.
23. Estandia, A., Harris, A. S. and Ford, T. J., Jr. Suppression of ventricular ectopic rhythms of parasympathomimetic drugs. *Fed. Proc.*, 10: 40, 1951.
24. Garrey, W. E. The nature of the fibrillatory contraction of the heart. Its relation to tissue mass and form. *Am. J. Physiol.*, 33: 397, 1914.
25. Blumgart, H. L., Hoff, H. E., Landowne, M. and Schlesinger, M. J. Experimental studies on the effect of temporary occlusion of coronary arteries in producing persistent electrocardiographic changes. *Am. J. M. Sc.*, 194: 493, 1937.
26. Porter, W. T. Further researches on the closure of the coronary arteries. *J. Exper. Med.*, 1: 46, 1896.
27. Levy, A. G. The exciting causes of ventricular fibrillation in animals under chloroform anesthesia. *Heart*, 4: 319, 1913.
28. Leriche, R. and Fontaine, R. Chirurgie des nerfs du coeur. *Acta chir. scandinav.*, 70: 260, 1933.
29. Meneely, G. R., Stahlman, M., McCrea, F. R., Smith, L. E. and Smith, H. J., Jr. Ischemic and anoxemic damage to myocardial capillaries and its relation to shock, angina pectoris and myocardial infarction. *Fed. Proc.*, 5: 226, 1946.
30. Burchell, H. B. Adjustments in coronary circulation after experimental coronary occlusion, with particular reference to vascularization of pericardial adhesions. *Arch. Int. Med.*, 65: 240, 1940.
31. Porter, W. T. On the results of ligation of the coronary arteries. *J. Physiol.*, 15: 121, 1894.
32. Hirsch, C. and Spalteholz, W. Coronararterienund Herzmuskel: Anatomische und experimentelle Untersuchungen. *Deutsche med. Wchnschr.*, 33: 790, 1907.
33. Miller, J. L. and Matthews, S. A. Effect on the heart of experimental obstruction of the left coronary artery. *Arch. Int. Med.*, 3: 476, 1909.
34. Smith, F. M. The ligation of the coronary arteries: An electrocardiographic study. *Arch. Int. Med.*, 22: 8, 1918.
35. Coelho, E. and Rocheta, J. Recherches electrocardiographiques sur la ligature des arteres coronaires chez le chien. *Compt. rend. Soc. de Biol.*, 102: 203, 1929.
36. Clerc, A., Deschamps, P. N., Bascourret, M. and Levy, J. R. Remarques electrocardiographiques sur la ligature des arteres coronaires chez le chien. *Compt. rend. Soc. de Biol.*, 103: 223, 1930.
37. Feil, H. S., Katz, L. N., Moore, R. A. and Scott, R. W. The electrocardiographic changes in myocardial ischemia. I. The effects of ligation of the left descending coronary artery with and without occlusion of the inferior vena cava. *Am. Heart J.*, 6: 522, 1931.
38. Parade, G. W. Die arterielle Blutversorgung des Herzens und ihre Storungen. *Ergebn. inn. Med. u. Kinderh.*, 45: 337, 1933.
39. Cox, W. V. and Robertson, H. F. Effect of stellate ganglionectomy on the cardiac function of intact dogs and its effect on the extent of myocardial infarction and on cardiac function following coronary artery occlusion. *Am. Heart J.*, 12: 285, 1936.
40. Harris, B. R. and Hussey, R. The electrocardiographic changes following coronary artery ligation in dogs. *Am. Heart J.*, 12: 725, 1936.
41. Gross, L. and Calef, B. Electrocardiographic changes in the dog following sudden occlusion of the left anterior descending coronary branch under various experimental conditions. *Am. Heart J.*, 14: 677, 1937.
42. Blumgart, H. L., Gilligan, D. R. and Schlesinger, M. J. Experimental studies on the effect of temporary occlusion of coronary arteries. *Am. Heart J.*, 22: 374, 1941.
43. Yodice, A. Sympathectomy and experimental occlusions of a coronary artery. *Am. Heart J.*, 22: 545, 1941.
44. Schauer, G., Gross L. and Blum, L. Hemodynamic studies in experimental coronary occlusion. *Am. Heart J.*, 14: 669, 1937.
45. Meneely, G. R., Stephenson, S. E., Jr. and Kochtitsky, O. M. The efficacy of quinidine in preventing ventricular fibrillation induced by temporary coronary artery occlusion in dogs. *Am. J. Med.*, 9: 262, 1950.
46. Meneely, G. R., Anderson, J. S., Hibbitt, L. L., McCarty, J. E., Stephenson, S. E., Jr., Young, E. R. and Ball, C. O. T. Evaluation of drug protection against experimentally induced ventricular fibrillation in 499 dogs. Quinidine,

procaine, pronestyl, xylocaine, trasentine, pendiomide, and Ciba #1194. *Fed. Proc.*, 11: 106, 1952.

47. Gold, H: Quinidine in Disorders of the Heart. New York, 1950. Paul B. Hoeber, Inc.
48. Harris, A. S., Estandia, A., Ford, T. J., Jr. and Tillotson, R. F. Quinidine lactate and gluconate in the suppression of ectopic ventricular tachycardias associated with myocardial infarction. Control of toxicity by morphine. *Circulation*, 4:522, 1951.
49. Hepburn, J. and Rykert, H. E. Use of quinidine sulphate intravenously in ventricular tachycardia. *Am. Heart J.*, 14: 620, 1937.
50. Schwartz, S. P. and Jezer, A. Action of quinine and quinidine on patients with transient ventricular fibrillation. *Am. Heart J.*, 9: 792, 1934.
51. Stephenson, S. E., Jr. and Main, B. F. Prevention of ventricular fibrillation in the normothermic and hypothermic heart. III. Advantage of quinidine over atriocaval block. *Surg. Forum*, 7: 278, 1957.
52. Rakov, H. L. Ventricular fibrillation in acute coronary thrombosis during the intravenous administration of quinidine sulphate, report of a fatal case. *Ann. Int. Med.*, 16: 571, 1942.
53. Kochmann, M. and Daels, F.: Wirkung des kokains auf das warmbluterherz unter besonderer berücksick tigung der extrasystole. *Arch. internat. pharmacodyn.*, 18: 41, 1908
54. Hermann, H. and Jourdan, F. Cocaine et syncope adrénalinochloroformique. *Compt. rend. Soc. de biol.*, 106: 1153, 1931.
55. Shen, T. C. R. and Simon, M. A.: Protecting action of novocaine upon chloroform-adrenalin ventricular fibrillation. *Arch. internat. pharmacodyn.*, 59: 68, 1938.
56. Burstein, C. L., Marangoni, B. A., DeGraff, A. C. and Rovenstine, E. A. Laboratory studies on the prophylaxis and treatment of ventricular fibrillation induced by epinephrine during cyclopropane anesthesia. *Anesthesiology*, 1: 167, 1940.
57. Stutzman, J. W., Allen, C. R. and Orth, O. S. Failure of procaine to reverse cyclopropane-epinephrine ventricular fibrillation. *Anesthesiology*, 6: 57, 1945.
58. Harris, A. S., Estandia, A., Ford, T. J., Jr., Smith, H. T., Olsen, R. W. and Tillotson, R. F. The effect of intravenous procaine and procaine amide upon ectopic ventricular tachycardia accompanying acute myocardial infarction. *Circulation*, 5: 551, 1952.
59. Kayden, H. I., Steel, J. M., Mark, L. C. and Brodie, B. B. Use of procaine amide in cardiac arrhythmia. *Circulation*, 4: 13, 1951.
60. Schaffer, A. I. Procaine amide compared with quinidine as a therapy for arrhythmias. *Am. Heart J.*, 42: 597, 1951.
61. Bellet, S., Zeeman, S. E. and Hirsh, S. A. Intramuscular use of Pronestyl (procaine amide). *Am. J. Med.*, 13: 145, 1952.

Recovery of Peripherally Injected Materials from the Heart at Varying Intervals after Death*

IRA N. ROSENSTEIN, M.D. *and* FRED WASSERMAN, M.D.

Coral Gables, Florida

THE APPROACHES to cardiac resuscitation are undergoing continuous modifications. Certain old and time-honored technics as thoracotomy (for cardiac massage), as well as intravenous and/or intracardiac Adrenalin® are undergoing modification and re-evaluation. Thus, Crowell, Sharpe and Lambright[1] have cast serious doubts on the use of intravenous epinephrine to supplement the effects of prolonged cardiac massage in attempts to resuscitate the fibrillating heart.

In addition to the introduction of new drugs and the re-evaluation of older drugs and mechanical technics, the routes of administration of various resuscitative agents have been re-examined and challenged. Kennamer and Prinzmetal,[3] in reviewing the therapeusis of cardiac arrhythmias, stated: "Since there is no circulation, it is difficult to understand the rationale of intravenous medication in cardiac asystole."

The present study was undertaken to determine whether peripherally injected materials do indeed reach the heart when given after cessation of electrocardiographic activity and termination of apparent blood flow.

METHODS AND MATERIALS

For this study three major methods were employed: (1) colorimetrically assayable dyes; (2) radioisotopes (radioiodinated human serum albumin-RISA); (3) roentgenography.

A total of seventeen mongrel dogs weighing between 4.5 kg. and 22.4 kg. were used. All animals were lightly anesthetized with intravenous sodium pentobarbital (1 grain per pound of body weight). The femoral artery and vein were isolated and heparinized cannulas passed about 0.5 cm. above the point of entry into the vessel. The distal ends of the cannulas were connected to three-way stopcocks. A two-channel electrocardiograph (Sanborn Twin-Viso Cardiette) was connected and continuous monitoring performed throughout the procedure. In ten dogs, simultaneous blood pressure recordings were obtained utilizing the cannula in the femoral artery and a Sanborn Transducer.

In two animals the chest was opened through the sixth left intercostal space from the left mid-posterior line to the left sternal border. Self-retaining retractors were then applied and separated to provide satisfactory exposure of the heart. The pericardium was dissected away from the beating heart. These animals were maintained on a mechanical respirator and given air through an endotracheal tube.

Death of the animals for the purpose of this study was defined as the cessation of all electrocardiographic activity, including ventricular fibrillation.

Dyes and RISA: T-1824 (Evans blue), bromsulphalein and 1 per cent phloxin-B dyes were used, as well as RISA. When the recommended dose of dye in terms of weight of dye per kg. body weight, was available, this was used. Thus, for T-1824 and bromsulphalein, the recommended doses were 0.35 mg./kg. body weight and 5 mg./kg. body weight, respectively. In the cases of phloxin-B and RISA, no such recommendation was available.

In order to give comparable total fluid volumes of test materials an arbitrary selection of 0.57 cc./kg. body weight was made.

With the exception of the thoracotomized animals, all dogs receiving T-1824, bromsulphalein or phloxin were managed as follows: under constant electrocardiographic monitoring, 15 per cent potassium chloride was injected slowly via syringe into the femoral vein until all electrical activity ceased. At two or four-minute intervals the dogs slowly received the test material injected into the femoral vein. Immediately thereafter, the chest was opened and,

* From the Departments of Medicine and Cardiology of the Veterans Administration Hospital, and the University of Miami School of Medicine, Coral Gables, Florida.

This study was aided by a grant from the United Better Health Foundation of greater Miami.

TABLE I

Time Sequence Between K^+ Death, Dye Administration and Roentgenograms

Dog No. and Dye	Film No. and View*	Time after Death (min.)	Dye Sequence	Site of Dye on Roentgenogram
14, 70% Urokon	1	2	Immediately after dye (0.5 total vol.)	Inferior vena cava to level of diaphragm
	2	3	1 min. after dye	Inferior vena cava—supradiaphragm
	3	4	2 min. after dye	Inferior vena cava and right atrium
	4	5	3 min. after 0.5 vol. 1 min. after full vol.	Right atrium and right ventricle
	5	6	4 min. after 0.5 vol. 2 min. after full vol.	Right atrium and right ventricle
15, 90% Hypaque-M	1	2	Immediately after dye	Inferior vena cava to level of 11th rib
	2	3	1 min. after dye	Inferior vena cava to level of 10th rib
	3	4	2 min. after dye	Inferior vena cava to level of 9th intercostal space
	4†	5	3 min. after dye	Inferior vena cava, right atrium and ventricle, superior vena cava
	5‡	6	4 min. after dye	Inferior vena cava, right atrium and ventricle, superior vena cava
16, 90% Hypaque-M	1	Antemortem	0 dye	Control
	2§	$3^1/_2$	$^1/_4$ dye vol.	Inferior vena cava to level of L1
	3§	5	$^3/_8$ dye vol.	Inferior vena cava to level of 11th rib
	4	9	$^5/_8$ dye vol.	Inferior vena cava and right atrium
	5	$10^1/_2$	Full dye vol.	Inferior vena cava and branches, right atrium right ventricle, superior vena cava
17, 70% Urokon	1	4	0 dye	Control
	2‖	$4^1/_2$	$^1/_5$ dye vol.	Inferior vena cava to level of L3
	3	$5^1/_2$	$^2/_5$ dye vol.	Inferior vena cava to level of L1
	4	7	$^4/_5$ dye vol.	Inferior vena cava to level of 10th rib
	5†	8	Total dye vol.	Inferior vena cava, right atrium and right ventricle
	6‡			

* All posteroanterior views except where indicated.
† Right lateral view.
‡ Left lateral view.
§ Burette drip; all others given by continuous syringe.
‖ Three and a half minute agonal state preceded four-minute death period.

using syringes with No. 22 needles, 5 cc. blood specimens were obtained from the right atrium, right ventricle, left atrium, left ventricle and femoral artery—in the order named. In several animals the superior and inferior venae cavae and pulmonary vessels were clamped prior to obtaining the blood specimens, but it was felt that the manipulation coincident with this produced a possible "milking" or reflux factor and therefore this particular approach was abandoned.

The infusion rates of the dye solution were as follows: (1) Dog 1 received the total dye solution at a rate of 4 cc./min. (2) Dogs 2 through 14 received their respective dye solutions at a rate of 1.5 to 2 cc. of solution per minute and dog 15 in two divided doses, each of 1.5 minutes' duration. (3) Dogs 16 and 17 received a constant infusion over ten and a half minutes and four minutes, respectively.

After a delay of thirty seconds from the end of delivery of the dye the chest was opened and the sampling from the cardiac chambers begun; the sampling itself required another three to five minutes.

RISA: Each of two dogs received 150 μc. of RISA injected into the femoral vein. The dose was diluted in normal saline to a total fluid volume equivalent to 0.57 cc./kg. body weight. A wide angle collimated scintillation detector was used with a recording high speed interval of four seconds, and a 3,000 full scale.

TABLE II

Summary of Mechanism of Death, Dye Employed, Injection Interval and Sites and Quantities of Dye Recovered

Dye	Dog No.	Mechanism of Death	Time after Death Dye Injected (min.)	Weight of Dog (kg.)	Volume of Dye (ml.)	Total Volume Fluid (ml.)	Per Cent Dye in the Following Sites				
							Right Atrium	Right Ventricle	Left Atrium	Left Ventricle	Femoral Artery
T-1824 (Evans blue)	1	15% KCl	4	22.4	1.56	12.80	1.5	1.5	0	0	0
	2	15% KCl	2	6.8	0.48	3.90	2.1	2.1	0	0	0
	3*	Electroshock	2	8.2	0.58	4.68	0.6	0.6	0	0	0
	4†	15% KCl	2	5.6	0.39	3.20	0	0	2.95	3.2	...
	5†	15% KCl	4	10.0	0.70	5.71	0	0	2.50	3.0	...
Bromsulphalein	6	15% KCl	2	8.1	0.80	4.60	4.5	3.0	0	0	0
	7	15% KCl	2	4.5	0.45	2.60	5.5	5.0	0	0	0
	8	15% KCl	4	6.4	0.64	3.70	4.0	3.0	0	0	0
	9	15% KCl	4	8.2	0.82	4.70	5.0	1.0	0	0	0
1% Phloxin-B	10	15% KCl	2	5.5	3.14	3.14	5.0	3.8	0	0	0
	11	15% KCl	4	5.9	3.37	3.37	1+	1+	0	0	0
RISA	12	15% KCl	2	5.9	150 μc. in 3.4 ml.: 18% at peak activity						
	13*	KCl Electroshock	2	7.3	150 μc. in 4.2 ml.: 5.3% at peak activity						

* Open chest antemortem. The remaining animals are closed chest.

† Site of dye injection: femoral artery. All others were injected into femoral veins.

There was a seven-second time constant and a high voltage of 680.

In the animal whose chest remained closed, two minutes after potassium chloride induced cardiac arrest, the RISA was injected and the detector held over the sternum at the level of the heart slightly to the left of the midline so as to act as if it were perpendicular to the sternum. In the animal whose chest was opened, two minutes after ventricular standstill, the RISA was injected. Here the detector was applied directly to the surface of the heart through the thoracotomy incision with the axis about ten degrees from the perpendicular. In each case, after the peak effect had occurred and subsided, a 10 μc. dose of RISA was given directly into the left ventricle and calibrations redetermined.

Roentgenography: In four dogs roentgenograms were obtained. In all the chest remained closed and arrest was potassium-induced. Two of the dogs received 70 per cent Urokon® and two received 90 per cent hypaque-M into the femoral vein. The sequence of injections and films are recorded in Table I.

Intra-Arterial Dye: In two dogs T-1824 was injected into the femoral artery with the chest closed. At two- or four-minute intervals after cardiac arrest, blood specimens were withdrawn from the cardiac chambers as previously described.

At the conclusion of each experiment, examination of the heart was made to rule out the presence of septal defects or other anomalies which might alter the results.

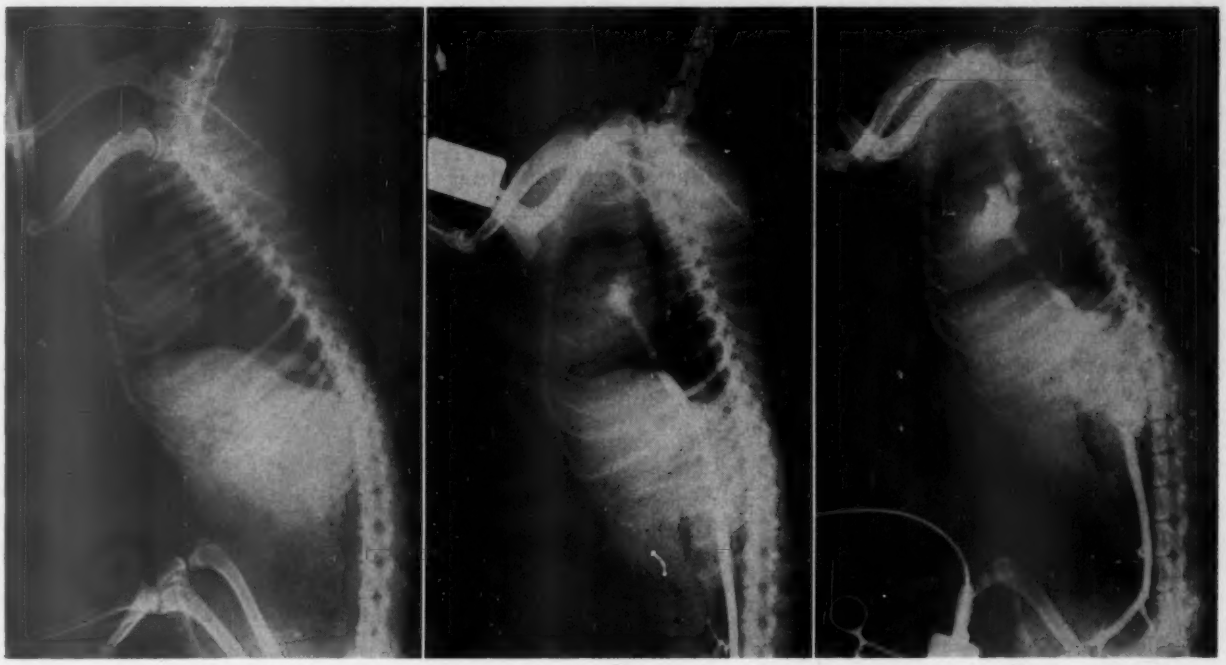
Results

The results obtained with the colorimetrically assayable dyes and with the radioisotope RISA are summarized in Table II which discloses the following:

(1) All materials given into the femoral vein reached both chambers of the right heart. None reached the left cardiac chambers.

(2) The aforementioned findings held true whether the material was diffusible merely within the extracellular fluids (as in the case with T-1824) or was so readily diffusible that it stained even the red blood cells (as in the case of 1 per cent phloxin-B in 1 M potassium chloride).

(3) All materials given intravenously reached the heart whether the chest was opened or closed, even when given as late as four minutes



A B C

FIG. 1. A, control subject: antemortem. B, postmortem passage of 90 per cent hypaque-M from femoral vein to right heart. Nine minutes postmortem: five-eighths total dye solution given by continuous administration. C, ten and a half minutes postmortem: total dye solution given.

after cessation of all electrocardiographic activity.

(4) The concentration of colorimetrically assayable dye was lowest in the dog whose chest was opened. Likewise, comparing the two dogs receiving RISA, the concentration of radioactive materials within the heart was significantly less in the animal whose chest had been opened.

(5) The concentration of intravenously injected material appearing in the right atrium was always as great as, and usually greater than, the concentration in the right ventricle.

(6) Intra-arterially injected dye appeared in both left cardiac chambers, but never in the right ventricular cavity. The concentration was greater in the left ventricle than in the left atrium.

(7) In each of the four series of roentgenograms there was demonstrated progressive passage of the dye from the site of injection at the femoral vein to the right atrium, right ventricle and even, apparently by reflux, into the superior vena cava. The full length of the inferior vena cava with many of its branches was likewise demonstrated. The sequence and results are given in Table I.

Figure 1 represents roentgenograms taken when 90 per cent hypaque-M was the radiopaque material employed (dog 16; Table I). Figure 1A shows control. Figure 1B clearly demonstrates the appearance of dye along the full length of the inferior vena cava and in the right atrium. This was taken nine minutes postmortem immediately after completion of the intravenous injection of hypaque solution given slowly over this nine-minute interval. Figure 1C demonstrates the appearance of the dye in both chambers of the right heart and the superior vena cava at ten minutes after death.

COMMENTS

The demonstration that peripherally injected intravenous materials reached the heart after death is of importance for at least several reasons: (1) intravenous attempts at cardiac resuscitation are widely used; and (2) such intravenous therapy, when indicated, might obviate the need for blind intracardiac injection with the attending hazard of hemopericardium and laceration of a coronary artery.

Our studies clearly demonstrate the ability of peripherally (intravenously) injected materials to reach the right heart. All technics employed uniformly demonstrated that both chambers of the right heart can be reached, and the dyes employed were repeatedly recovered in significantly measurable quantities. In addition, an

appreciable quantity of the injected material was demonstrated radiographically to regurgitate into the superior vena cava (Figure 1C). This may be important because: ". . . at the cephalic end of the sulcus terminalis in the notch formed by the junction of the superior vena cava and the auricle with the main atrial chamber,"[4] is found the nodal mass which is the primary pacemaker of the heart, i.e., the sino-atrial node. Likewise, the atrioventricular bundle which takes its origin from the atrio-ventricular node "begins in the septal wall of the (right) atrium a short distance in front of the coronary orifice."[4]

In every case, when the intravenously injected material was recovered, its concentration was equal to and most often greater in the right atrium than in the right ventricle. When, on the other hand, the dye was given intra-arterially, the concentration as might be expected was greater in the left ventricle than in the left atrium. In effect, the concentration appears to be greatest in that cardiac chamber nearest the site of injection.

In an open chest, with the increase in intrathoracic pressure (decrease in "negative" pressure), there is greater resistance to the passage of dye from the intravenous injection site to the right heart. This is best seen by comparing the difference in concentration of RISA in the open and closed chests at the peak of radioactivity. Because the cone employed "tapped" the great veins, as well as the heart itself, the per cent activity must be taken as a relative, rather than an absolute value. Nonetheless, the concentration in the closed chest is significantly greater.

Factors Affecting Venous "Transport" to the Heart Postmortem: Although the boundaries of the experimental protocol precluded any precise definition of those factors responsible for the recovery of peripherally injected material from the cardiac chambers, one might speculate on contributory factors.

Using a technic to maintain constant force and velocity, Phillips et al.[5] demonstrated that as venous pressure is increased, the resistance to flow in the isolated dog's hind leg is decreased. They concluded that passive dilation of vessels resulting from the increased intraluminal pressure (as with syringe injection) is the primary factor responsible for the decreased resistance. Passive mechanical factors may not be the sole contributors to "transport" of materials postmortem. There may, indeed, be active processes persisting which also provide their assistance. The persistence of venous return in the dying or fibrillating heart has been previously reported. Houssay[2] notes that despite absence of all blood pressure in the fibrillating or recently dead heart, the venous return is such as to permit recovery of at least 50 per cent of the total volume of blood from the heart. What is not currently known is how long this venous return persists after cessation of electrocardiographic activity. Our studies included administration of materials for at least as long as four minutes after the termination of electrocardiographic activity, with recovery of material from the right heart. While it is perhaps difficult to imagine persistence of venous return for longer than four minutes postmortem, the precise duration of venomotor tone after death remains to be documented.

Another factor intimately related to persistence of venous return appears to be the normal negative intrathoracic pressures. We have demonstrated that the relative amount of the test materials recovered in the closed chest is most often greater than in the open chest, where intrathoracic and atmospheric pressures have been equalized. Despite the fact that at the time of injection there were no respiratory movements to "milk" the materials up along the inferior vena cava, the mere presence of a passively existing gradient of pressure may serve an important postmortem function. It may be that if the animals whose chests remained closed had been maintained on artificial respiration, the per cent dye recovery would have been still greater.

Whatever the mechanisms of "transport," it obtained in our studies so that materials injected as much as four minutes postmortem into a peripheral vein reached both chambers of the right heart and refluxed into the superior vena cava.

Summary

1. Employing colorimetrically assayable dyes, radioisotopes and radiopaque materials we have demonstrated that these materials, given into peripheral veins at varying intervals postmortem, reach the right side of the heart.

2. The effectiveness of intravenous administration is greater in the closed chest where "negative" intrathoracic pressures persist than in the open chest.

3. Possible factors to explain this postmortem "transport" are discussed.

References

1. Crowell, J. W., Sharpe, G. P. and Lambright, R. L. Prolonged massage of the fibrillating heart. *Surgery*, 42: 701, 1957.
2. Houssay, B. A. Human Physiology, 1st ed., p. 210. New York, 1951. McGraw-Hill.
3. Kennamer, R. and Prinzmetal, M. Treatment of cardiac emergencies. *M. Clin. North America*, p. 1313, September 1956.
4. Morris, H. Human Anatomy: A Complete Systematic Treatment, 10th ed., p. 596. Philadelphia, 1951. The Blakiston Co.
5. Phillips, F. A., Brind, S. H. and Levy, M. N. The immediate influence of increased venous pressure upon resistance to flow in the dog's hind leg. *Circulation Res.*, 3: 357, 1955.

Franz Groedel Memorial Lecture

The History of Coronary Sclerosis*

PAUL KLEMPERER, M.D., SC.D. (HON.)
New York, New York

WHEN I selected my topic for this Memorial Lecture, I was well aware that most competent medical scholars had already chosen the same subject for historic analysis. I had two reasons for deciding to repeat their review. First, for years I have been fascinated by the study of the evolution of our present day knowledge of coronary sclerosis and have tried to perceive the interplay between the observation of facts and their rational interpretation, which has led to our present concept with its accomplishments as well as its unsolved questions. Second, the medical historian working in an area which has been studied so thoroughly cannot expect to discover new historical information from the writings of the past; but he might connect the recorded facts in a manner different from that of his predecessors and throw sharper light on the various facets of a complex medical problem.

In a recent article by Kennan[1] I came upon the following sentence: "No work of history ever begins soon enough or ends late enough to be wholly rounded." The history of coronary sclerosis is no exception to this statement. Where shall one begin and when shall one end?

HEBERDEN AND HIS PRECURSORS

If we try to unravel the twisted story of the evolution of our present day concept it might be well to take up the thread with Heberden's[2] classic description of angina pectoris. Then we shall be able to trace the strands back to preceding pertinent observations and clearly discern subsequent disclosures as they contributed to the comprehension of the complicated problem of coronary sclerosis. Heberden's first report was made to the College of Physicians in London in July 1768 and was published in the second volume of the Society's *Medical Transactions* in March 1772. This report was based upon twenty clinical observations and he stressed at its beginning and at its end that "this disorder of the breast has not yet found a place or a name in the history of diseases." It would be amazing that the dramatic clinical picture he described should not have attracted the attention of physicians in preceding times. Indeed, Heberden asserts that "when I first took notice of this distemper and could find no satisfaction from books, I consulted an able physician of long experience who told me that he had known several ill of it and all of them had died suddenly." This remark gives us some insight into Heberden, the medical investigator. In the tradition of Sydenham, he depended on personal observation, but as a scholar he was well aware of the value of the study of literature which he affirms when he recommends to the young physician the perusal of observations and reports of learned societies. But those reports in which he might have found support for his own observations were probably not available to him. There is good presumptive evidence for this assertion if one reads the list of treatises which he recommends to his son in his "Introduction to the Study of Physic."[3] It does not include these essays from which subsequent medical historians selected observations more or less relevant to angina pectoris (Marx,[4] Sternberg,[5] Gibson,[6] Kohn,[7a,b] Warburg,[8] Dock[9]

* Sixth Franz Groedel Memorial Lecture, on the Humanities in Medicine, delivered at the Eighth Annual Meeting of the American College of Cardiology, May 27, 1959, Philadelphia, Pennsylvania.

and Herrick[10]). I have studied the original references, with the exception of those of Petraglia, quoted by Kohn, which was not available to me. It would be repetitious to review them again in detail but I want to add some records which have not been considered before, or only very casually, and remark on others which, I believe, are not pertinent.

Bartholin[11] was probably well aware of sudden cardiac death because he states that "the cause of apoplexy is not always to be looked for in the brain. Sometimes it lies in the obstructed vessels of the heart due to arrested blood." In his treatise on sudden death, Lancisi,[12] in the chapter on the signs of future sudden death due to the heart, the large vessels and the blood, cites an observation of Hollerius, 1498–1562, of a seventy year old man with pain in the heart, angor animi and attacks of suffocation who died suddenly. He refers to the Hippocratic aphorism that "cardiac pain frequently attacking old people foretells sudden death" and mentions a patient of his own who died unexpectedly in such an attack. On the same page he quotes Hippocrates, who recognized an association of gastric and cardiac pain with sudden death.

In addition to the frequently mentioned case of Morgagni,[13] Letter 26, Observation 31 of the forty-two year old family mother, I call attention to his Case 13 in Letter 42 which has not found consideration probably because the autopsy report is silent about the heart but describes only renal changes pointing toward a calculous pyelonephritis. Yet the detailed clinical history strongly suggests the diagnosis of angina pectoris. It concerns a man beyond the age of sixty, who suffered attacks of cardiac pain which forced him to stop walking. The attacks became more severe over a period of a few years, with pain around the sternum and numbness of the left arm. He died in one of his attacks. Finally, the observation of Marcello Malpighi[14] in 1677 which, while quoted by Morgagni, has not been included in the historic reviews mentioned above. It is that of an elderly man who suffered for three years of intermittent severe pain around the sternum and left arm associated with precordial oppression, and in whose body at autopsy the heart was found to be twice the normal size. These reports indicate that the syndrome of angina pectoris was at least noticed by physicians prior to Heberden, but I believe that the observations of Ballonius[15] and Case 92 of Hoffmann,[16] both quoted by Kohn, should be omitted because of ambiguity.

The clinical symptoms in all other cases could have reminded Heberden of those in his own observations, but they were only sketchy case reports from which a concise clinical entity could not have been abstracted. There is, however, one longer account most pertinent to his description, but it had not attracted the attention of the medical profession and was unearthed only after Heberden had rendered his classical report. Fabrizio Bartoletti, 1576–1630, gave on four pages of his "Methodus in Dyspnoeam"[17a] a detailed description of a clinical syndrome which conforms, in the main, with that of angina pectoris. Because the Anglo-Saxon literature pays little attention to this precursor of Heberden I have translated the chapter from the original Latin and submit some of the most pertinent passages:

"I proceed therefore to the description of the characteristic features of this dyspnoea from which sudden death can be predicted. Those who have respiratory difficulties pointing toward sudden death show no perceptible cause of such distress. There is no evidence of pulmonary involvement; the patients are not hydropic nor do they suffer from laboured breathing, nor of asthma; all these signs are absent. Yet they have respiratory difficulties when walking and they are forced to stop because they experience a sort of suffocation, accompanied by a certain annoying sensation around the sternum which is indescribable and gradually ascends towards the jugulum. Rest only is the remedy for this distress, and if at rest the patients appear well." This is the description of the acute attack. Then follows another observation: "The patients can lie down on either side and when they think they are at rest, they are suddenly forced up and have to walk up and down, not merely to sit up." After giving some other details, he turns to the personality of the patients: "They are dissatisfied with themselves and with others, very ill humored and easily angered and annoyed."

One might ask why this lucid description was completely disregarded after its publication. The lack of autopsy reports accounts for the neglect by Morgagni, whose immortal work is so replete with references to previous authors. Why did it escape the attention of the great cardiologists of the seventeenth and eighteenth century, Vieussens, Lancisi, Albertini and Senac? One of the reasons might well have been the lack of interest in exact diagnosis which characterized medical thinking of that period, with the exception of Sydenham. The

aim was to establish general systems through which a comprehension of diseases could be achieved with the corollary of a universal therapy. Iatrochemical and iatromechanical systems were developed and clinical observation was pursued with the sole purpose of fitting the individual patient into the general scheme of the system. Exact nosography could not develop well in such a climate of thought which might account for the neglect of Bartoletti's clear description of the syndrome of angina pectoris. The fact that it was included as a short chapter in a compendious treatise on dyspnea must have added to the obscurity of its significance. Finally, the lack of necropsy experiences prevented the anatomically and physiologically oriented physician of his and subsequent periods from noticing this important clinical discovery. Whatever the reasons are, Bartoletti's contribution was completely disregarded and Heberden is the undisputed discoverer of angina pectoris, were it not for the peculiar claim of French medicine to give priority to Rougnon,[17b] who published his letter to Lorry on February 26, 1768, five months before Heberden's presentation. After perusal of the original, I can only fully agree with Hans Kohn's scholarly refutation[7b] of this claim of priority.

In his first communication on angina pectoris, Heberden had regretfully remarked on his inability to perform an autopsy on any one of his patients and had given as a tentative explanation for the symptoms "a strong cramp or an ulcer or possibly both."[18] The lack of necropsy information was soon to be eliminated. He received a letter dated April 16, 1772 in which the anonymous writer refers to an extract of his article which had appeared in the previous issue of the *Critical Review*. This magazine, also entitled *Annals of Literature by a Society of Gentlemen*, was a monthly book review edited by Tobias C. Smollett, a retired physician, which had published in its March issue a detailed abstract with favorable comments of Heberden's article on angina pectoris which had been published in 1772. This letter contains the most accurate description of the symptoms of the illness of which the letter writer had been suffering. It is, indeed, the best record by a lay person, more concise than the previous account[19] by Hyde of the illness of his father, the Earl of Clarendon, and far less ambiguous than Seneca's letter[20] to Lucilius which some later medical authors, including Osler, believed to indicate that the philosopher suffered from angina pectoris. At the end of the letter the correspondent informed Heberden of his decision to have his body examined in case of his anticipated sudden death. Less than three weeks later Heberden was notified that the patient had died during a walk which he had taken after dinner.

Heberden[21] "procured that experienced and accurate anatomist, Mr. J. Hunter, to open the body," but, "upon the most careful examination no manifest cause of his death could be discovered; the contents of the thorax were examined with peculiar attention, particularly the heart with its vessels and valves and were all found to be in a natural condition. The left ventricle of the heart was remarkably strong and thick."[22] The coronary vessels are not mentioned and we know on the authority of Jenner[23] that they were not inspected. From this autopsy Heberden drew the conclusion[24]: "This anatomical examination, though it does not inform us what the cause of the disease was, will, however, have its use by informing us what it was not. For since it was not owing to any mal-conformation or morbid destruction of parts necessary to life, we need not despair of finding a cure." And in a letter[25] to Percival he wrote: "The dissection of this sufferer by the angina pectoris as well as that of a few others which I heard of teaches us that the disease is neither owing to inflammation nor to any mal-conformation of the parts."

John Fothergill

The absence of anatomic changes supported Heberden's opinion that the cause of angina pectoris was a spasm, to which he referred again in his "Commentaries,"[26] but he left open its exact localization. While the pathologic-anatomic account was equivocal, the clinical description was so precise that angina pectoris was soon generally accepted as a sharply defined morbid entity. The first confirmation came from Fothergill in 1776 in the report[27] of a case "of that kind which is so fully and judiciously described by Dr. Heberden; a disease which I had too often met with as it terminated for the most part fatally and without its being in my power in one single instance to learn from dissection the seat of it." In this instance Fothergill had obtained authorization for postmortem examination which was performed by the Drs. Langley, "judicious surgeons in the neighborhood." It disclosed in the heart "not the least ossification or appearance of disease, except on the outward muscular part, near the apex a small white spot, as big as a sixpence, resembling a cicatrix." There was bilateral hydrothorax. A report of the second case, that of a sixty-three year old man, whose autopsy was performed by

Hunter, was published in the same year. There was also hydrothorax.

"The substance of the heart was paler than common, more of a ligamentous consistence and in many parts of the left ventricle it was become almost white and hard, having just the appearance of a becoming ossification. The two coronary arteries from their origin to many of their ramification upon the heart were become one piece of bone."

In discussing the necropsy findings Fothergill stresses the accumulation of fluid in the thorax, the unusual quantity of fat around the heart and the scarlike appearance of the myocardium. He is aware of their pathognomonic significance and predicts that "in future dissections these three praeternatural appearances will be found." He has little to say about correlation of the clinical symptoms with the anatomic alterations and even less regarding their meaning for the pathogenesis of angina pectoris except that he recommends restriction in diet.

Jenner and Parry and Coronary Ossification

Within the subsequent years the medical profession became more and more familiar with the disease as described by Heberden through individual case reports (Wall,[28] Johnstone,[29] Home[30] (the case of Hunter) and Black[31]). By the end of the century Parry[23] added three new observations to the seven already recorded. This distinguished physician of Bath, however, was not satisfied with mere repetitious description but entered upon an analysis and explanation of the pathogenetic problems presented by the clinical and anatomic observations. The central point of his interpretation is stated on page 60 of his essay:

"I think it is evident that the angina pectoris is in reality a case of fainting: The syncope genus 44 of Dr. Cullen's nosology which he defines to be the motion of the heart diminished or even for some time ceasing. The patient probably dies with no other symptoms than those which shew an irrevocable diminution of the motion of the heart."

Parry was guided in his studies by the experience of his friend Jenner, whom he consulted in reference to the pathologic anatomic findings and who wrote[23] him "as to the series of observations which produced his opinion that the angina pectoris arose from some morbid structure of the heart, which change was probably ossification or some similar disease of the coronary arteries."

Ossification or petrification of the coronary arteries was not an entirely new observation and its possible effect upon heart action had already been commented upon by Bellini[32] more than a hundred years before when he spoke "of pressure of stones upon the trunk and larger branches of the coronaries which may lead to arrest of the motion of the heart and an intermittent pulse." Drelincourt,[33] Thebesius,[34] Lancisi,[35] Crellius,[36] Haller,[37] Morgagni[38] and Senac[39] had published individual similar observations. The idea of clinical-anatomic correlation between narrowing of coronary arteries and functional cardiac disability was not deeply rooted and in the few pre-Heberdenian cases[12–17] of the anginal syndrome referred to above, changes in the coronary artery were not mentioned. Parry's comment on the frequency of ossification of the coronary artery is significant. After a thorough review of the literature he concludes:

"It appears then that from the whole mass of medical and anatomical writers previously to the last edition of Senac's treatise on the heart in 1773 not more than twelve or fourteen instances can be collected, in which the coronary arteries were found ossified; but that, since that period, seven instances have been seen of obstructed coronaries, in six of which they were ossified; all in cases of angina pectoris, and four actually predicted."

Parry, however, was not content with the factual knowledge of a coincidence of angina pectoris and coronary ossification. He tried to comprehend the pathogenesis of the disease, its course and its characteristic symptomatology, pain and angor animi. He was not the first who entertained the idea that the symptoms of angina pectoris and death of the patients were due to failure of the heart. Johnstone,[29] in 1787, spoke of "defect of power in the heart" as the cause of the illness of his patient. The state of the coronary vessels is not mentioned in his autopsy report, but we find the following description of the heart:

"... very putrid, admitting my finger passing through it with very little pressure." He stressed in his conclusion "that such a state must render it unfit for its office of carrying on the circulation of the blood, or in other words, of supplying life." However, "from what causes, or cause the putridity or disposition to mortification which seized this vital muscle, arose, may not be very clear."

Black, in his case report of 1795, described the heart to be "unusually tender and lacerable" and "the two coronary arteries exhibiting the

most complete ossification I ever saw." He assumes that the heart was in a state of functional disability and that "the pain can clearly be referred to the heart as its seat," giving as explanation: "it is a fact very generally observed, that when an organ is, by disease, rendered unfit for its office, the performance of that office is attended by pain." He also noticed a striking dilatation of the aorta from its origin to its curvature which indicated to him also an evidence of functional liability. Wall[28] found ossified aortic valves at the autopsy of one of the twelve to thirteen patients whom he had observed clinically. He remarked that:

". . . the blood must have been propelled into the aorta with great difficulty; and probably part of it regurgitated again into the ventricle during the systole of the artery." While "he is not certain that this induration of the semilunar valves is always the cause of the disease,. . . he is inclined to imagine that a praeternatural induration of the parts necessary to the circulation through the heart may be praedisponent if not the efficient cause of the disease."

While these references indicate that the central position of the heart in the pathogenesis of angina pectoris was recognized by some observers, it was not obvious to those who ranked among the authorities of that period. It has already been mentioned that Heberden thought rather vaguely of a functional, spastic rather than an organic disorder as the cause of the disease. Hunter, although he had seen coronary ossification in one of Fothergill's patients, seemed not to have recognized its significance. This is evident from Parry's remark[40] that "he says nothing of it in any of his lectures and publications." This lack of appreciation of the importance of the organic lesion explains the touching attitude of Jenner expressed in his letter to Heberden[41] which prevented him from publishing his conviction that coronary ossification is responsible for angina pectoris. "I am fearful (if Mr. Hunter should admit this to be the cause of the disease) that it may deprive him of the hopes of a recovery." While Parry deserves no priority he must be credited with having marshalled all the available evidence for the coronary ischemic theory of angina pectoris. His cogent conclusions illustrate how, at the end of the eighteenth century, conceptual generalizations were arrived at by persistent correlation of clinical and anatomic data and how observational empiricism through statistical reasoning succeeded in abstracting the general law for the comprehension of morbid phenomena. Important also is his endeavor to associate the crucial symptoms, pain and angor animi with morbid function. He believed that the pain is due to distention of the heart resulting from accumulation of blood engendered by inadequacy of muscular power, the anxiety to the lack of aeration of the blood. Parry compares the uneasiness one feels if one holds the breath with a similar sensation resulting from compression of both carotid arteries.

Allan Burns and Muscle Ischemia

It is true that Parry's explanation of the mechanism of pain production in angina pectoris is no longer tenable today, but it seems to me that for the evolution of concepts in medicine the answer is less important than the raising of the right question. The right answer came soon enough from a brilliant young physician, Burns,[42] who died soon after its publication.[43] He was convinced of the fundamental significance of coronary sclerosis in angina pectoris, but did not accept the reasons proposed to account for the pain. Neither Parry's satisfied him, nor the one offered by Home, who believed that the nerves of the spastically contracted heart muscle are pressed against the rigid coronaries. He rejected this assumption with the following statement: "I am afraid that this is too mechanical an explanation of the mode of induction of this painful sensation; and I think it is hardly corroborated by any analogous fact in the animal economy." He submits his own hypothesis founded upon clinical and anatomic observation and most admirable reasoning and proves it by experiment. It had been taken for granted since Morgagni[44] that the identity of structure of cardiac and voluntary muscle presupposes identity of function. Burns, therefore, investigated the effect of moderate ligation of a limb upon muscle action and finds[45] that "the member can only support its action for a very short time." This experience leads to his first conclusion:

"A heart the coronary vessels of which are cartilagineous or ossified is in nearly a similar condition; it can, like the limb begirt with a moderately tight ligature, discharge its function so long as its action is moderate and equal. Increase, however, the action of the whole body and along with the rest that of the heart and you will soon see exemplified the truth of what has been said." In reference to pain he described "the unusual painful feeling in the limb after application of a tourniquet only so tight as to impede the circulation."

Pain as the result of muscular ischemia was

clearly recognized by Burns. Lewis' work,[46] published more than 100 years later, rests on Burns' remarkable induction. It is, therefore, amazing that Lewis gives credit to Potain[47] for having first pointed to ischemia as the cause of anginal pain in analogy to the pain in intermittent claudication.

Nineteenth Century Concept of Angina Pectoris

In 1809, thanks to the observations and deductions of Jenner, Parry and Burns, the concept of cardiac ischemia due to narrowing of the coronary arteries seemed to be well established as the cause of angina pectoris, but it was not generally accepted. Angina pectoris as a clinical entity was recognized all over Europe but its pathogenesis was still an unsolved problem which was ardently discussed throughout the nineteenth century. No doubt Heberden's authority weighted heavily in favor of a spastic origin and the seat of the spasm was localized either in the heart (Latham[48]) or in the cardiac nerves (Desportes[49]). There were logical reasons why organic lesions in general and those of the coronary arteries in particular seemed not to give a satisfactory explanation. It was argued that paroxysmal attacks with intervals of well-being could not be compatible with a permanent anatomic alteration. Parry tried to meet the objection by indicating [50] that:

"In reality, these organic disorders may be considered within certain limits mere predisposing causes; that is which produce such a degree of the proximate cause, as does not constitute apparent disease, but requires, for this effect, the cooperation of some remote, and, as it is usually termed, exciting cause."

Is this statement not reminiscent of the modern concept of coronary insufficiency? Another objection against the coronary theory was the apparent inconstancy of the occurrence of vascular ossification. On one hand it was maintained that some patients with angina pectoris did not show narrowing of the coronary arteries at autopsy, and on the other hand it was noted that even severe coronary obliteration was not always associated with anginal symptoms during the life of the patient. This contention was satisfactorily answered only when accurate examination of the coronary arteries became a command for the pathologic anatomist. Parry had already asserted[51] that "no negative proof (i.e., of coronary artery integrity) can in future be admitted unless the examination be made in the manner which I have proposed."

It took more than a century until adequate methods for perfusion[52] were developed for determining exactly the sufficiency or insufficiency of the circulation of the coronary arteries according to the state of the vascular system in the cadaver. Correlative studies of experimental vascular occlusion and electrocardiographic changes[53] in conjunction with clinical-pathologic investigations[54] have resulted in a remarkably high degree of statistical certainty of diagnosing and even localizing coronary artery occlusion. To establish directly the site and extent of vascular sclerosis in the individual patient still awaits further research. Attempts have been made most recently to determine them by means of ultrasound. Certainly Parry's and Jenner's thesis has been fully vindicated more than a century after it had been proposed.

Aortic Lesions and Angina Pectoris

If we return to the early decades of the last century we meet another reason why their conclusions were rejected. The increasing number of autopsies disclosed conspicuous anatomic lesions different from coronary ossification. For instance Testa[55] refers to the case of a man, thirty-four years old, who had all the symptoms of angina pectoris and at whose autopsy a ruptured aortic aneurysm was found. This observation supported his contention that no constant anatomic lesion can be regarded as solely responsible for the syndrome of angina pectoris. Today the relationship between syphilitic aortitis and interference with the coronary circulation is too well known to dwell upon it. But in 1826 when Testa published his book this relation was not known, although aortic insufficiency with the characteristic separation of the cusp in association with aortic arch aneurysm was clearly illustrated by Figure 1 of Hodgson's work.[56] Corrigan[57] recognized the relationship between "permanent patency of the aorta" and the anginal syndrome but was not aware of the significance of the concomitant aortic changes although the description of two of his patients is most suggestive of luetic aortitis in the light of present knowledge. Blackall[58] was most impressed by the dilatation of the aorta and the severe alteration of its inner coat. He follows Pratt's idea that the organic changes might be the result of primary aortic spasms, an idea which was revived many decades later by Albutt[59] and Wenkebach.[60] He describes particularly striking aortic lesions around the coronary ostia but does not consider them as impor-

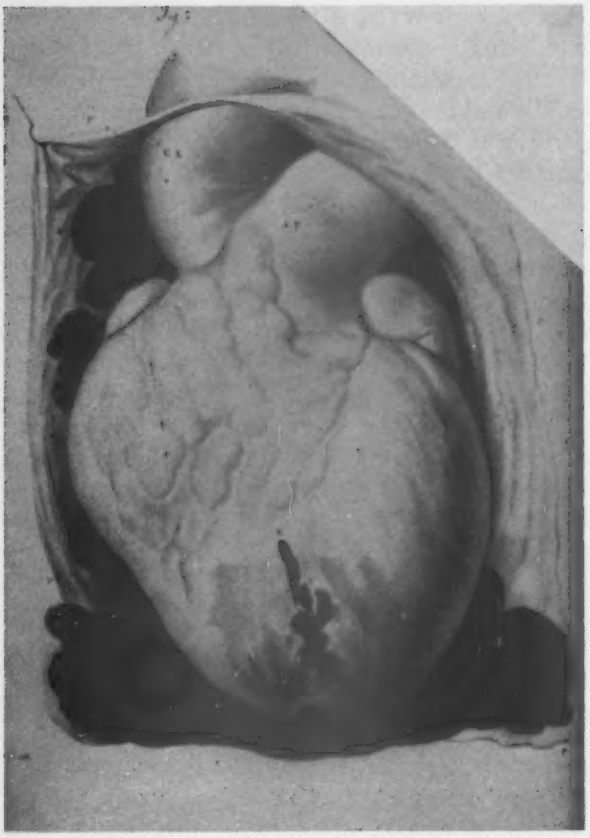


FIG. 1. From Cruveilhier, J.[70a], Planche II, Fig. 2. Spontaneous rupture of the heart.

FIG. 2. From Cruveilhier, J.[70a], Planche III, Fig. 1. Apoplexy of the heart.

tant. The aorta in his patient too was "thickened and dilated from the heart to the diaphragm, its inner surface lying in folds and wrinkles," a description which arouses the suspicion of syphilitic aortitis. In this case no attention was paid to the coronary arteries because "this case happened before the publication of Dr. Parry's very ingenious work."

This apparent diversity of anatomic findings in angina pectoris served to deemphasize Jenner's and Parry's notion and to support the neuralgic hypothesis of the symptom complex. More generally, it was apt to reduce even further the possible significance of changes of the coronary arteries upon alterations of the function and structure of the heart.

RUPTURE OF THE HEART

It is amazing that a dramatic observation like rupture of the heart had hitherto remained unexplained and in particular, that it had not been connected with changes of the coronary arteries. It had first been described by Harvey[61] and it is noteworthy that the patient had been suffering for some time of an oppressive pain in the chest. Harvey ascribes the rupture to an obstructed transit of blood from the left ventricle into the arteries and parenthetically remarks that its wall was normally thick and strong. In contrast, Morand,[62] a century later, states that the fibers had become soft in one of his patients with cardiac perforation. Morgagni was well acquainted with the condition and reported some personal observations and those of others in the twenty-seventh and sixty-fourth letters, but no mention is made of the state of the coronary arteries.

Hodgson[63] was the first to notice and accurately describe as completely obliterated a branch of the left coronary artery leading to a rent in the apex of the heart. In discussing the case Hodgson refers to obstruction of the arteries as a frequent cause of mortification in senile gangrene of the extremities which had been described and illustrated by John and Cowper[64] in 1702 and by Naish[65] in 1721. Hodgson's discussion discloses the new dynamic trend which entered into pathologic anatomy at the beginning of the nineteenth century. The mere parallelism of clinical symptoms and anatomic findings which was still characteristic of Morgagni's master work gradually yielded to a tendency to explain the changes of structure. The data established at the autopsy table by exact observation were submitted to critical analysis to determine the causal factors. Hunter's idea to search for the evolution of the pathologic lesion, i.e., for the morbid process, became the guiding principle of modern pathologic anatomy.

This new scientific orientation transpires in Abercrombie's[66] preface to his "Pathological and Practical Researches on Diseases of the Brain" when he states: "The value of general statements

of a physician in regard to the phenomena of disease depends in a very great degree upon the character which he bears as a philosophical observer." Abercrombie[67] and Rostan[68] were the first to recognize arterial obstruction as the cause of encephalomalacia. The new strategy of investigations in morbid anatomy took root only slowly and Hodgson's explanation of cardiac rupture was not even mentioned in Stokes'[69] and other textbooks of cardiology appearing in the middle of the nineteenth century. Cruveilhier[70a] gave exquisite illustrations of rupture and apoplexy of the heart in his famous "Atlas" (Figs. 1 and 2) but did not refer to the coronary arteries. Yet the brilliant physiologist and physician, Hall,[71] in a Gulstonian lecture of 1842 attributed sudden death in many instances to an interruption of the coronary circulation. This remark persuaded Ehrichsen[72] to test the hypothesis experimentally. He concluded that arrest of the coronary circulation causes a speedy cessation of the heart's action and remarked on the obvious bearing these results have on the cause of death in cardiac failure. This is the first of a series of experiments which have contributed much to clarifying the influence of the coronary circulation on cardiac function in human disease.

Recognition of Myocardial Changes in Coronary Sclerosis

It is clear that the dramatic anatomic picture of cardiac rupture attracted the attention of observers more than the less impressive alterations of the myocardium characterized by mere changes in its consistence and color. Nevertheless, Crellius[73] in his description of an ossified coronary artery, refers to the heart as decayed and soft and in the early reports of autopsies on patients who had angina pectoris one reads of the heart being tender and friable (Black,[81] Johnstone,[29] Parry's patient Bellamy[23]). No questions were raised to account for this condition. With the increasing tendency of pathologic anatomists not to limit themselves to mere description, but to ask for the reason of the structural alteration, and with the introduction of the microscope into investigations of pathology, these morbid changes came under close scrutiny. In 1850, Quain[74] established in unequivocal terms the relationship between coronary obstruction and degenerative states of the myocardium and presented excellent correlation between the clinical signs of angina pectoris and the findings at autopsy. At the same time Virchow[75] refers to:

> "... the well known processes in the myocardium which produce these peculiar yellowish and greenish discolorations through fatty metamorphosis and softening of the muscle substance" and states that "on accurate preparation one can often enough ascertain affected segments of the coronary arteries in exact correspondence with the morbid muscular portions." In his "Handbuch"[76] he wrote that "the sudden obstruction of the coronary arteries seems to produce a sudden paralysis of the heart as extreme form of Heberden's angina pectoris."

Virchow's Concepts of Thrombosis

From then on the interest of pathologic anatomy began to focus upon the dependency of myocardial alterations on obliteration of the coronary arteries with emphasis upon sudden occlusion. For centuries already intravascular blood coagulation had attracted the attention of anatomists; for centuries the notorious polyp of the heart and large vessels had been a topic of polemic. In 1674 Bartholin[11] wrote that apoplexy may sometimes be due to arrest of blood in the vessels of the heart. He believed[77] that the cause of the concretion of the blood was its inspissation due to lack of water derived from the lymphatics. One might look upon this interpretation as the first theory of thrombosis. Under the influence of Hewson and Hunter intravital intravascular blood coagulation was regarded as the result of vasculitis and Cruveilhier[78] formulated this idea with the words: "The first effect of arteritis as well as phlebitis is coagulation of the blood."

This doctrine was repudiated through Virchow's classical pathologic-anatomic and experimental investigations on thrombosis and embolism which extended over a period of nearly eleven years. He separated the three factors which are responsible for thrombosis: alteration of the vascular wall, alteration of the blood constitution and retardation of the blood current. Since that time our knowledge of the mechanism of intravascular coagulation has greatly increased but our concept still rests fundamentally on Virchow's principles and present day research on coronary thrombosis can still trace its inspiration to Virchow's clear definition. It may be well to insert here that forty years ago Libman pointed out[80] that:

> ... the tendency to thrombosis was something apart from the tendency to get arterial disease. Atherosclerosis of the heart and brain was very much

FIG. 3. From Carswell, R.[70b], Plate III, Fig. 2. Description by Carswell: Figure 2 represents four aneurysms (F, G, H and K). D, pericardium united to heart by firm cellular tissue. E, the cellulo-fibrous tissue which formed from the fibrine of the blood, and toward this part the cavity of the ventricle is sensibly dilated.

FIG. 4. From Carswell, R.[70b], Plate III, Fig. 3. Description by Carswell: Figure 3 represents the ventricles of the heart laid open by a transverse section. E, the pericardium intimately united to the heart by firm cellular tissue. F, columnae carneae the lining membrane of which and the subcellular tissue present the same pale yellow colour, opacity, and loss of elasticity as in the other cases. The greater part of the left ventricle was replaced by a tissue, in some parts of a fibrinous, in others of a cellulo-fibrous or fibrous character, thus indicating the gradual transformation of the fibrine of the blood into fibrous tissue.

more frequent than the occurrence of thrombosis in such arteries. It was important, therefore, to discover what caused the tendency to thrombosis in certain individuals and what could be done to prevent the condition."

These prophetic words were spoken by a great clinician steeped in pathologic anatomy twenty years before the introduction of anticoagulants into the therapy of coronary thrombosis and they are still a challenge today.

Myocardial Fibrosis and Chronic Myocarditis

There was still another frequent myocardial alteration, whose relationship to coronary artery sclerosis now became the object of pathologic anatomic investigation, the myocardial fibrosis, commonly regarded as chronic myocarditis, and partial cardiac aneurysm.[81] In 1559 Columbus[82] wrote that he had seen the interventricular septum of the heart to be cartilagenous. In the same century Thuanus[83] reported that he had found an ossification of the left ventricle at the necropsy of Count Schomberg, who had died suddenly. Veslingius[84] saw a "cartilagenous crust covering the inside of the left ventricle extending into the aorta." Morgagni[85] quotes Albertini, who had seen in some bodies "that the substance of the heart from the basis to more than half its extent had become tendinous, both in consistence and colour." He has seen it himself[86] and concludes[87] "that the force of the heart decreases so much the more in proportion as the greater number of its parts become tendinous instead of being fleshy." He doubts, however, that this cardiac alteration is the cause of sudden death although he knows of the report of Thuanus regarding the death of Count Schomberg. Baillie[88a] described very exactly partial aneurysm of the left ventricle of the heart. The two autopsy reports on Fothergill's patients[27] refer to cardiac changes which can only be interpreted as myocardial fibrosis.

For decades such lesions were regarded as evidence of chronic myocarditis. Carswell[70b] (Figs. 3 and 4) and Cruveilhier[70a] (Fig. 5) gave exquisite illustrations in their "Atlas" without reference to the coronary arteries. Rokitansky (cf. Loebl[88b]) and even Virchow did not think of a pathogenetic association with obstruction of the coronary arteries. Only when acute myomala-

cia was clearly understood and its frequent combination with myocardial fibrosis was noticed did a correct interpretation become established. Thus, in the third quarter of the last century the pathogenetic synthesis of the different myocardial alterations in their relation to coronary artery sclerosis was completed. Several essays published around the year 1880 presented exact anatomic observations and rational conclusions which in broad outline reflected a concept which corresponds with today's point of view. Weigert,[89] Ziegler[90] and Huber[91] are generally regarded as those who first clearly formulated the basic idea. It would be an injustice to omit mention of Loeb,[92] who in a doctoral dissertation of 1880 from the Rindfleisch Pathological Institute in Würzburg gave a comprehensive thesis of "Malacia Cordis" in its relation to coronary occlusion, and of Lanceraux'[93] remarks in his treatise. A comparison of these articles with the more ancient reports previously mentioned illustrates the evolution of a concept in pathology. It originated in sporadic observations like that of Harvey[61] on rupture of the heart and Columbus'[82] on myocardial fibrosis. Such individual records were systematically collected by Morgagni,[94] but their inter-relationship and the mechanism of their origin were not considered. This reflects the static, descriptive phase of medical thinking. The observations of Cowper[64] and Naish[65] that senile gangrene is the result of reduced blood supply would have remained only a limited experience had not Rostan[68] and Abercrombie[67] recognized the general principle by the analogy with acute encephalomalacia which gave Hodgson[63] and particularly Quain[74] and Virchow[75,76] the clue for the interpretation of the softening of the heart muscle.

The use of analogy for scientific explanations is not highly appreciated today but in the early days of scientific investigations of coronary sclerosis it was of creative value by suggesting an experimental approach to support an interpretation of the pathogenetic mechanism which was founded upon analogous anatomic observations. The validity of this assertion is obvious for the pathologic anatomy of coronary sclerosis and thrombosis. Our present understanding of anginal pain rests also on the analogy with the production of pain in the exercised ischemic voluntary muscle, an analogy which was clearly recognized and utilized by Burns[43] 120 years before Lewis.[46] Pathologic anatomic investigations had now circumscribed the morbid entity of coronary sclerosis. Of course, further inquiry was necessary to clarify fully puzzling variations and persistent research with improved technics, such as postmortem perfusion of the coronary system[52,54] and histopathologic studies of the atherosclerotic plaque in its relation to arterial occlusion (Paterson[95]), brought important additional information.

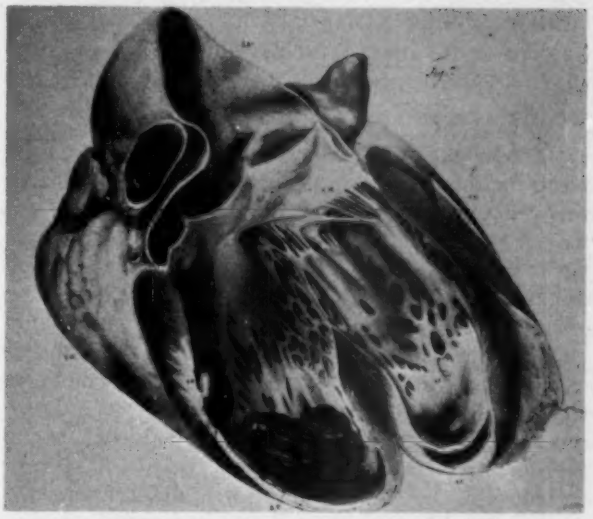


FIG. 5. From Cruveilhier, J.[70a], Planche III, Fig. 2. Partial true aneurysm of the heart occupying the apex of left ventricle.

Clinical Recognition of Sequelae of Coronary Sclerosis

The next objective was to establish the corresponding entity on clinical grounds. This task met considerable obstacles which are hardly comprehensible to the physician of today. Historically, the clinical concept of coronary sclerosis begins with Jenner and Parry, not with Heberden. Parry believed that the existence of coronary ossification could be predicted from the clinical features of angina pectoris; but the link between autopsy findings and bedside observations was tenuous. He was aware that coronary ossification was not the proximate cause of the anginal syndrome and assumed a weakness of the heart without anatomic foundation. Burns' illumination could have clinched the clinical concept of obstruction of the coronary arteries but the time was not yet ripe to comprehend the significance of his observation and it was disregarded. Moreover, the broader aspects of coronary sclerosis, such as coronary thrombosis and the cardiac sequelae, had not been recognized anatomically and, therefore, could not be suspected on clinical grounds. While there is some evidence in the light of present knowledge that some of the early recorded

cases of patients with angina pectoris might have died of acute myomalacia, there is no question that in 1846 Latham[48] noticed it clinically. In the discussion of the first patient he writes:

"There was nothing extraordinary in this case so far as the mere symptoms were concerned. But there was still a circumstance in the case which was new to me: The brief period that intervened (fourteen days) between the paroxysm first denoting the patient's disease and the paroxysm of which he died." The second patient died ten days, the third a few hours after the first attack. These were the clinical circumstances, which, he stated "added something at least to my knowledge of the disease." At autopsy, the heart in Cases 2 and 3 was extremely soft, of the first "not softened in an extreme degree." Severe coronary ossification was found in this patient, apparently healthy vessels in the second and a conspicuous narrowing of a single coronary artery in the third.

While Latham perceived the distinctive clinical features and the unusual cardiac alterations, the examination of the coronary arteries was inadequate, which precluded a valid clinical-anatomic correlation and, thus, the delineation of a morbid entity separate from angina pectoris. In fact, Latham did not accept Jenner's and Parry's ischemic theory but believed in spasm of the heart as the proximate cause. His discerning clinical observations, therefore, could not promote a deeper comprehension of acute coronary artery occlusion.

The pathologic-anatomic reports of myocardial alterations resulting from coronary artery sclerosis and thrombosis generally included short references to clinical symptoms in the subsequent decades. However, they were not detailed enough to permit the abstraction of a precise clinical picture of the various sequelae of coronary artery sclerosis observed at the autopsy table. Hammer's[96] introductory remarks to his report of thrombotic occlusion of a coronary artery reflect the state of information which existed in 1878 regarding the clinical problem:

"At the autopsy table, thrombosis and embolism of the coronary arteries have often enough been demonstrated. During life, however, a thrombosis of both or one of these vessels, has so far not been observed or at least not been recognized."

A few years later, von Leyden[97] stressed the urgency of a clinical delineation of the pathologic-anatomic entity and presented the first classic nosography of coronary sclerosis. A full comprehension of the clinical problem was retarded because of the erroneous generalization which Cohnheim and Schulthess-Rechberg[98] reached from their experiments. Their assumption that coronary arteries are terminal vessels and that their ligation irrevocably causes death prevented the realization that coronary artery thrombosis in man is not always fatal. Through the experimental results of preceding and subsequent investigators (Amenomiya[99]), this error was corrected. An increasing number of careful clinical-anatomical observations unequivocally demonstrated that thrombotic occlusion of even major trunks of the coronary arteries was compatible with survival. This point of view was already expressed by Krehl[100] in an article in Nothnagel's "Handbook" at the turn of the century. But it is Herrick[101] to whom the credit must go for having fully awakened the medical profession to the significance of the clinical problem of coronary sclerosis and thrombosis. With rare discernment and inspiring persistence he assembled his unequivocal observations until he had convinced the medical world of the reality of his conclusions. The practical viewpoint of coronary thrombosis is best epitomized with his own words:[102] "It is essential to think of this condition as a possibility and to rid the mind of the notion that such a diagnosis is possible only at necropsy." His optimism was soon vindicated. The introduction of electrocardiography has raised the diagnosis from statistical anticipation to exact recognition determined by objective signs of functional disability of the cardiac muscle.

It is with just pride that we survey these achievements of the labor of generations, the results of an interplay of exact bedside and autopsy observations and rational thought. But in our satisfaction we must not forget that the riddle of coronary sclerosis has not yet been solved. "It would be an object valuable in a more important view than that of mere philosophical curiosity, could we discover the cause of that ossification, which seems to produce the disease and so many others of a dangerous kind." It seems to me appropriate to quote these words[103] at the end of my historical review to illustrate that the crucial problem of coronary sclerosis was recognized by Parry 160 years ago but is still awaiting its solution today. Here is where the past merges with the future.

References

1. Kennan, G. F. It's history, but is it literature? *New York Times Book Rev.*, p. 35, April 26, 1959.
2. Heberden, W. Some account of a disorder of the

breast. *M. Tr. Coll. Physicians, London*, 2: 59, 1772.

3. Cummons, de R. An Introduction to the Study of Physic by William Heberden. *Ann. Med. Hist.*, 10: 349, 1928.
4. Marx, K. F. H. Über die Anfälle mit dem Gefühle des Verscheidens, dem intermittierenden Herzschmerz, das Leiden des Philosophen Lucius Annaeus Seneca. *Abhandl. d. Kgl. Gesellsch. d. Wissensch. zu Göttingen*, 17: 3, 1872.
5. Sternberg, M. Das Chronische Partielle Herzaneurysma. Leipzig und Wien, 1914. F. Deuticke.
6. Gibson, G.A. The nervous affections of the heart. *Edinburgh M. J.*, 12: 9, 1902.
7. (*a*) Kohn, H. Angina pectoris. *Ergebn. ges. Med.*, 9: 209, 1926.
   (*b*) Kohn, H. Zur Geschichte der Angina Pectoris. Heberden oder Rougnon. *Ztschr. klin. Med.*, 106: 1 1927.
8. Warburg, E. J. Über den Coronarkreislauf und über die Thrombose einer Coronararterie. Anatomie, Physiologie und Historik. *Acta med. Scandinav.*, 73: 425, 1930.
9. Dock, G. Historical notes on coronary occlusion. *J. A. M. A.*, 113: 563, 1939.
10. Herrick, J. B. A Short History of Cardiology, chapt. IX. Springfield, Ill., 1942. Charles C Thomas.
11. Bartholin, T. De Anatomia Practica Consilium, p. 41. Hafniae, 1674. Sumptibus Petri Houbaldi.
12. Lancisi, J. M. De Subitaneis Mortibus, p. 74. Romae, 1707. Typisi F. Baugni.
13. Morgagni, J. B. The Seats and Causes of Diseases, vol. I, pp. 819–820; vol. II, pp. 484–486. Translated by Benjamin Alexander. London, 1769. A. Millar & T. Cadell.
14. Malpighi, M. Opera Posthuma, p. 62. Amstelodami 1700. Apud Donatum Donati.
15. Ballonius, G. Consiliorum Medicinalium, Libri II, Consilium XXVIII, p. 71. Parisiis, 1635. Apud J. Quesnel.
16. Hoffmann, F. Consultationum et Responsorum Medicinalium. Centuria Prima, Complectens Morbos Capitis et Pectoris, vol. I, Casus 92. Frankfurt, 1734. F. Varrentrapp.
17. (*a*) Bartoletti, F. Methodus in Dyspnoeam, Liber IV, Pars IV, Cap. III, p. 383. Bononiae 1633. Per Heredes Evangelistae Dozzae.
   (*b*) Rougnon. Lettre a M. Lorry. Besancon, 1768. J. F. Charmet.
18. Heberden, W.[2] p. 64.
19. Rosenbloom, J. To the editor. *Ann. Med. Hist.*, 4: 210, 1922.
20. Quoted from Parry.[23]
21. A letter to Dr. Heberden concerning the angina pectoris; and an account of the dissection of one, who had been troubled with that disorder. *M. Tr. Coll. Physicians, London*, 3: 1, 1774.
22. A letter to Dr. Heberden concerning the angina pectoris; and an account of the dissection of one, who had been troubled with that disorder. *M. Tr. Coll. Physicians, London*, 3: 8, 1774.
23. Parry, C. H. Inquiry Into the Symptoms and Causes of the Syncope Anginosa, Commonly Called Angina Pectoris. Illustrated by Dissections, p. 3. London, 1799. Cadell & Davis. (Jenner's letter to Parry.)
24. Heberden, W. 1774, l.c. p. 9.
25. Percival, T. The Works, vol. IV, pp. 191–194. London, 1807. J. Johnson.
26. Heberden, W. Commentaries on the History and Cure of Diseases, Chapt. 70. London, 1802. T. Payne.
27. Fothergill, J. The Works, vol. II, pp. 249–268. London, 1783. C. Dilly.
28. Wall, J. A letter from Dr. Wall to Dr. Heberden on the same subject. *M. Tr. Coll. Physicians, London*, 3: 12, 1785.
29. Johnstone, J. Case of angina pectoris from an unexpected disease of the heart. *Mem. M. Soc. London*, 1: 376, 1787.
30. Home, E. Introduction. In: John Hunter's Treatise on the Blood, Inflammation, and Gun Shot Wounds. London, 1794. G. Nicoll.
31. Black, S. Case of angina pectoris with remarks. *Mem. M. Soc. London*, 4: 261, 1795.
32. Bellini, L. Opera Omnia, p. 449. Venetiis, 1732. J. G. Hertz.
33. Drelincourt Quoted from Bonetus Sepulcretum, Editio Altera. Liber I, Sectio XII, Additamenta Obs. VIII. Lugduni, 1700. Genevae, Cramer & Perachon.
34. Thebesius, A. C. Dissertatio Med. de Circulo Sanguinis in Corde, p. 7. Editio Nova Correctior. Lugduni Batavorum. 1740. G. Potvliet.
35. Lancisi, J. M. De Motu Cordis et Aneurysmatibus. Opus. posthumum. Romae, 1728. J. M. Salvioni.
36. Crellius, J. F. De Arteria Coron. Instar Ossis Indurata Observatio. 1740 in Disputationes ad Morborum Historiam et Curationem Facientes. Edited by Haller, A. Lausanne, 1757. M. M. Bousquet et Soc.
37. Haller, A. Opuscula Pathol., Observat. 50 and 51. Lausanne, 1755. M. M. Bousquet & Soc.
38. Morgagni, J. B.[13] letter 24, art. 16.
39. Senac, J. Traité de la Structure du Coeur, de son Action et de ses Maladies, vol. II, 2nd ed., p. 402. Paris, 1774. Vincent.
40. Parry, C. H.[23] p. 107.
41. Baron, J. The Life of Edward Jenner, p. 40. London, 1838. H. Colburn.
42. Herrick, J. B. Allan Burns 1781–1813. Anatomist, Surgeon and Cardiologist. *Bull. Soc. M. Hist. Chicago*, 4: 459, 1935.
43. Burns, A. Observations on Some of the Most Frequent and Important Diseases of the Heart. Edinburgh, 1809. Bryce & Co.
44. Morgagni, J. B.[13] Ep. 25, art. 13.
45. Burns, A.[43] p. 142.
46. Lewis, T. Pain in muscular ischemia. Its relation to anginal pain. *Arch. Int. Med.*, 49: 713, 1932.
47. Potain, C. Anemie. In: Dictionnaire Encyclopedique des Sciences Medicales, vol. 4, pp. 346–348. Paris, 1870. P. Asselin, V. Masson et Fils.
48. Latham, P. M. Lectures on Subjects Connected with Clinical Medicine, Comprising Diseases of the Heart. London, 1846. Longman.
49. Desportes, E. H. Traité de L'angine de Poitrine, ou Novelle Recherches sur une Maladie de la Poitrine, que L'on a Presque Toujours Confondue

avec L'asthme, les Maladies du Coeur etc. Paris, 1811. Crapelet.
50. Parry, C. H.[23] p. 111.
51. Parry, C. H.[23] p. 110.
52. Gross, L. The Blood Supply to the Heart in its Anatomical and Clinical Aspects. New York, 1921. P. B. Hoeber, Inc.
53. Smith, F. M. The ligation of coronary arteries with electrocardiographic study. *Arch. Int. Med.*, 22: 8, 1918.
54. Blumgart, H. L., Schlesinger, M. J. and Davis, D. Studies on the relation of the clinical manifestations of angina pectoris, coronary thrombosis and myocardial infarction to the pathologic findings. *Am. Heart J.*, 19: 1, 1940.
55. Testa, A. G. Delle Malattie del Cuore, vol. III, p. 187. Napoli, 1826. Torchi di Raffaello.
56. Hodgson, J. Engravings Intended to Illustrate some of the Diseases of Arteries Accompanied with Explanations. London, 1815. T. Underwood.
57. Corrigan, J. On aortitis as one of the causes of angina pectoris. With observations on its nature and treatment. *Dublin J. M. Sc.*, 12: 243, 1838.
58. Blackall, J. Observations on the Nature and Cure of Dropsies, and Particularly on the Presence of the Coagulable Part of the Blood in Dropsical Urine, to Which is Added an Appendix, Containing Several Cases of Angina Pectoris. London, 1814. Longman.
59. Allbutt, C. Diseases of the Arteries, Including Angina Pectoris. London, 1915. Macmillan Co.
60. Wenkebach, K. F. Klinik und Wesen der Angina Pectoris. *Wien. med. Wchnschr.*, 74: 621, 1924.
61. Harvey, W. Opera Omnia a Collegio Medicorum, p. 127. Londinensi edita, London, 1766. G. Bowyer.
62. Morand, M. Sur quelques accidents remarquables dans les organes de la circulation du sang. *Mem. Acad. roy. sc.*, pp. 428–434, 1732.
63. Hodgson, J. A Treatise on the Diseases of Arteries and Veins. London, 1815. T. Underwood.
64. Evelyn, J. and Cowper, W. An account of divers schemes of arteries and veins. *Philos. Tr*, 23°. 1777, 1194, 1702.
65. Naish, E. Concerning an ossification of the crural artery. *Philos. Tr.*, 31: 266, 1721.
66. Abercrombie, J. Pathological and Practical Researches on Diseases of the Brain. Philadelphia, 1831. Carey & Lea.
67. Abercrombie, J.[66] p. 45.
68. Rostan, L. Recherches sur le Ramollissement du Cerveau. Paris, 1823. Béchet Jevne.
69. Stokes, W. The Diseases of the Heart and the Aorta. Dublin, 1854. Hodges & Smith.
70. (*a*) Cruveilhier, J. Anatomie Pathologique du Corps Humain, Livraison 22, Planche III, Figs. 1 and 2; Livraison 3, Planche I, Fig. 1. Paris, 1829–1835. J. & B. Baillière.
(*b*) Carswell, R. Hypertrophy. In: Pathological Anatomy, Plate III, Figs. 2 and 3. London, 1838. Longman.
71. Hall, M. The Mutual Relations between Anatomy, Physiology, Pathology and Therapeutics and the Practice of Medicine. Gulstonian Lecture. London, 1842. H. Baillière.
72. Ehrichsen, J. E. On the influence of the coronary circulation on the action of the heart. London *M. Gaz.*, (n.s.) 2: 561, 1841–42.
73. Crellius, J. F.[36], p. 566.
74. Quain, R. On fatty diseases of the heart. Medico-Chir. Tr., (Sec. ser.) 15: 121, 1850.
75. Virchow, R. Ernährungseinheiten und Krankheitscheerde. *Arch. path. Anat.*, 4: 375, 1852.
76. Virchow, R. Handbuch der speciellen Pathologie und Therapie, p. 173. Stuttgart, 1854. Erlangen u Stuttgart, F. Enke.
77. Bartholin, T. De Lacteis Thoracicis in Homine Brutisque Nuperrime Observatis Historia Anatomica, Chapt. XIV, pp. 64–65. Trajecti ad Rhenum, 1654. Typis Gisberti A Zyll. & Theod. Ad Ackersdijck.
78. Cruveilhier, J.[70a] 3rd installment, p. 5.
79. Virchow, R. Gesammelte Abhandlungen zur wissenschaftlichen Medicin. Frankfurt A. M., Meidinger, 1856. Sohn & Comp.
80. Libman, E. Some observations on thrombosis of the coronary arteries. *Tr. A. Am. Physicians*, 34: 138, 1919.
81. Sternberg, M. Das chronische partielle Herzaneurysma. Anatomie, Klinik, Diagnose. Leipzig & Wien, 1914. F. Deuticke.
82. Columbus, M. R. De re Anatomica, libri XV, p. 265. Venetiis, 1559. Ex Typis N. Bevilacqae.
83. Thuanus, J. A. Historiarum sui Temporis Tomus V, Liber 12d, Sect. 9 p. 814. London, 1733. S. Buckley.
84. Veslingius, J. Observationes Anatomicae et Epistolae Medicae ex Schedis Posthumis Selectae et editae a Th. Bartholino. Hafniae, 1664. Apud Petrum Hauboldum.
85. Morgagni, J. B.[13] Ep. 27, art. 17.
86. Morgagni, J. B.[13] Ep. 45, art. p. 636.
87. Morgagni, J. B.[13], p. 640.
88. (*a*) Baillie, M. The Morbid Anatomy of Some of the Most Important Parts of the Human Body, p. 26. London, 1793. J. Johnson.
(*b*) Loebl, G. De aneurysmate cordis sic dicto partiali. Dissert. Inauguralis 1840, Vindobonae.
89. Weigert, C. Über die pathologischen Gerinnungsvorgänge. 1880.
90. Ziegler, E. Über myomalacia cardis. *Arch. path. Anat.*, 90: 211, 1882.
91. Huber, K. Über den Einfluss der Kranzarterienerkrankungen auf das Herz und die chronische Myocarditis. *Arch. path. Anat.*, 89: 236, 1882.
92. Loeb, J. Über partielle erweichende Myocarditis (Malacia cordis). Inaugural Dissertation. Würzburg, 1880.
93. Lancereaux, E. Traite D'anatomie Pathologique, p. 820. Paris, 1879–81. V. A. Delahaye & E. Lecrosnier.
94. Morgagni, J. B.[13] Ep. 27, art. 2 & 10, & ep. 64, art. 14/15.
95. Paterson, J. C. Factors in the production of coronary artery disease. *Circulation*, 6: 732, 1952.

96. Hammer, A. Ein Fall von thrombotischem Verschluss einer der Koronararterien des Herzens. *Wien. med. Wchnschr.*, 28: 100, 1878.
97. Von Leyden, E. Über die Sklerose der Coronararterien und die davon abhängigen Krankheitszustände. *Ztschr. klin. Med.*, 7: 458,539, 1884.
98. Cohnheim, J. and Von Schulthess-Rechberg, A. Über die Folgen der Kranzarterien verschliessung für das Herz. *Arch. path. Anat.*, 85: 503, 1881.
99. Amenomiya, R. Über die Beziehungen zwischen Koronararterien und Papillarmuskeln im Herzen. *Arch. path. Anat.*, 199: 187, 1910.
100. Krehl, L. Die Erkrankungen des Herzmuskels und die nervösen Herzkrankheiten, in Nothnagel Hermann. Specielle Pathologie und Therapie, p. 369. Wien, 1901. A. Hölder.
101. Herrick, J. B. Clinical features of sudden obstruction of the coronary arteries. *J. A. M. A*, 59: 2015, 1912.
102. Herrick, J. B. Thrombosis of the coronary arteries. *J. A. M. A*, 72: 387, 1919.
103. Parry, C. H.[23] p. 132.

Report on Therapy

Comparison of Laxative Action of Bisacodyl Suppositories and Glycerin Suppositories in Acute Myocardial Infarction*

JULES LEVINE, M.D. *and* SEYMOUR H. RINZLER, M.D.
New York, New York

INCREASING attention is being directed toward the problem of maintaining bowel function in patients with acute myocardial illness.[1–3] Several factors in the treatment of acute myocardial infarction may induce bowel problems even in patients with no prior history of constipation. Spasms of the bowel may be evoked by narcotics given to control pain, by apprehension of the patient concerning exertion and by fear associated with the illness itself. In addition, patients unaccustomed to a bedpan may be hindered in evacuating by improper muscular coordination.

We believe with Kitchell[2] that in these patients care of bowel function should begin in the first days of treatment. We have previously[1] stated our opinion that attention to the distal end of the colon is sufficient to relieve the acute problem of constipation after myocardial infarction. In this regard, we agree with Almy and Steinberg[4] that the "ideal cathartic, that which most closely simulates the natural mechanism of defecation, would act on no portion of the bowel other than the distal colon."

A new laxative agent, bisacodyl† acts on direct contact with the colonic mucosa, and does not depend on systemic absorption for its effect. Administration of a rectal suppository containing 10 mg. of bisacodyl is reported to induce evacuation of normally formed, soft stools usually within fifteen to sixty minutes, without undesirable side effects.[5–7] Pharmacologic[8] and clinical[9] evidence indicates that bisacodyl induces peristalsis by specific reflex stimulation of the parasympathetic nerves of the colon, but that it is without effect on other segments of the gastrointestinal tract or on other organ systems under parasympathetic control.

In determining the activity of a laxative agent in patients, Greiner, Bross and Gold[10] have indicated the desirability of comparing the test compound with a standard agent. It is, therefore, the purpose of this study to compare laxative suppositories containing 10 mg. of bisacodyl with glycerin suppositories in patients with acute myocardial infarction.

MATERIAL AND METHODS

The trial was carried out as follows: When a laxative was first required by a patient, a bisacodyl or glycerin suppository (U.S.P.) was arbitarily chosen for administration and a suppository of the other type was administered only if a bowel movement failed to occur within two hours. If neither laxative compound was effective after two hours, an enema was employed. On succeeding occasions when a laxative was required, the order of administration was reversed. Thus on each trial occasion bisacodyl or glycerin suppositories were administered, but both were used only when the first failed to produce an effective bowel movement. In this way, data could be gathered on the effectiveness of each laxative used initially and used after the failure of the other compound. Furthermore, the design of the study as-

† Bisacodyl (Dulcolax®) suppositories and glycerin suppositories (U.S.P.) for this study were supplied by Geigy Pharmaceuticals, Ardsley, New York.

* From the Medical Service, Beth Israel Hospital, New York, New York.

TABLE I

Response of Twenty Patients with Myocardial Infarction to Repeated Trials of Bisacodyl and Glycerin Suppositories

	Bisacodyl					Glycerin				
	Total	Success		Failure		Total	Success		Failure	
		No.	Per Cent	No.	Per Cent		No.	Per Cent	No.	Per Cent
First suppository	37	28	75.7	9	24.3	41	18	43.9	23	56.1
Second suppository	22	19	86.4	3	13.6	9	3	33.3	6	66.7
Total	59	47	79.7	12	20.3	50	21	42.0	29	58.0

sured that these acutely ill patients always receive an effective laxative agent when it was needed.

There were a total of seventy-eight occasions for laxative trial in twenty patients selected for the trial. All of the patients studied had a history of arteriosclerotic heart disease and were suffering from acute myocardial infarction at the time of the trial. The group included seventeen men and three women, ranging in age from thirty-eight to seventy-nine years. Although there was seldom a prior history of constipation, all were acutely constipated at the beginning of the laxative trial, presumably because of the administration of narcotics or because of difficulties in using the bedpan. Laxative treatment was initiated by the third day after the onset of infarction in more than half of the patients, by the eleventh day in the rest, except for one patient who was first given one of the trial laxatives on the seventeenth day after onset. None of the patients were in shock or congestive heart failure at the time of the trial, and none had had a spontaneous bowel movement.

In order to minimize bias in the evaluation of the two agents, the bisacodyl and glycerin suppositories provided for the trial were indistinguishable in appearance, and were labeled only by code. The true identity of the two types of suppository was not known to the investigators until after the results of the trials had been evaluated in all patients.

A special form was used to record observations on the time required for the suppositories to act, the amount and consistency of the stools and any untoward effects associated with the use of the two agents.

Results

During the course of the study, a suppository containing 10 mg. of bisacodyl was administered initially in thirty-seven instances when laxative treatment was required, while a glycerin suppository was administered initially in the remaining forty-one instances. As shown in Table I, a bowel movement occurred promptly in 75.7 per cent of the trials with bisacodyl, and in 43.9 per cent of the trials with glycerin suppositories. This difference proved to be statistically significant ($P < 0.01$) on analysis by the chi-square test.

There were thirty-two occasions when the initial laxative suppository failed to produce a bowel movement within two hours. In all but one of these cases, the other type of suppository was then administered. A glycerin suppository produced a bowel movement in three of the nine occasions when it was used after bisacodyl had failed to act. Conversely, bisacodyl induced prompt evacuation on nineteen of twenty-two occasions (86.4 per cent) when patients failed to respond to glycerin suppositories. The chi-square test showed that the superior response to bisacodyl in these refractory cases was likewise statistically significant ($P < 0.01$).

Thus, bowel movement occurred in 79.7 per cent of a total of fifty-nine occasions on which bisacodyl was used, compared to 42 per cent of a total of fifty occasions on which glycerin suppositories were used.

TABLE II

Time Required for Response to Laxative Suppositories

Approximate Interval (min.)	No. of Trials	
	Bisacodyl	Glycerin
15	1	1
30	11	2
45	12	1
60	8	6
75	4	3
90	4	1
Over 90	2	3
Totals	42	17

TABLE III
Consistency of Stools after Trials of Different Laxatives

Consistency	No. of Trials	
	Bisacodyl	Glycerin
Hard	13	6
Soft	26	9
Loose	2	2
Watery	2	0
Totals	43	17

The time required for evacuation after the administration of bisacodyl or glycerin suppositories is indicated in Table II for fifty-nine occasions in which the suppositories were used successfully. The mean time was fifty-two minutes for bisacodyl and sixty-three minutes for glycerin suppositories.

The consistency of the stools on sixty occasions after the use of the trial suppositories is indicated in Table III, which shows no substantial difference between the two suppositories in this respect; soft, formed stools resulted in a majority of instances with either compound.

Undesirable reactions were observed occasionally with both preparations. After the administration of glycerin suppositories, abdominal cramps were reported by one patient in one of two trials with the compound; griping was reported by one patient on the only occasion the preparation was used; and sweating was observed once in a third patient. After the use of bisacodyl suppositories, cramps or griping occurred on three occasions in one patient, and on one occasion in eight others, along with increased sweating in one. Slight abdominal pain was reported on two occasions, and tenesmus once during the trial. There were no untoward events attendant upon the insertion of a suppository rectally.

Comments

In planning the care of patients during acute myocardial infarction, it is necessary to select measures which will accomplish their purpose without creating additional burdens of stress for the patient. This is particularly true in choosing a laxative agent to counteract the constipation that commonly occurs in these patients. The results of this study indicate that suppositories containing bisacodyl may be quite well suited to the special requirements of such patients. Bisacodyl proved to be much more consistently effective than glycerin suppositories in our patients, and usually produced a normal evacuation of soft, formed stools within an hour after administration.

Although most of our patients received bisacodyl repeatedly during a period of several weeks, no tendency for the development of tolerance to or habitual use of this agent was observed. While cramps and griping were observed on several occasions, these transient undesirable effects were usually mild and did not cause undue stress to the patient.

Summary

A new laxative agent, bisacodyl, was compared with glycerin suppositories in the bowel care of twenty patients with acute myocardial infarction. In a total of 109 trials with one or both agents, bisacodyl was effective in 79.7 per cent, while glycerin suppositories were effective in 42 per cent.

Few undesirable reactions were observed with either agent, and none were severe. Bisacodyl appears to be well tolerated and quite reliably effective in treating constipation associated with acute myocardial infarction.

References

1. Rinzler, S. H. The Clinical Aspects of Arteriosclerosis, p. 194. Springfield, Ill., 1957. Charles C Thomas.
2. Kitchell, J. R. General considerations in treatment of myocardial infarction. *Am. J. Cardiol.*, 1: 224, 1958.
3. Dennison, A. D., Jr. Use of dioctyl sodium sulfosuccinate in cardiovascular disease; correction of bowel function. *Am. J. Cardiol.*, 1: 400, 1958.
4. Almy, T. P. and Steinberg, H. The choice of drugs for gastro-intestinal disturbances. In: Drugs of Choice, p. 388. Edited by Modell, W. St. Louis, 1958. C. V. Mosby Co.
5. Scott, J. E. S. A new laxative. *Practitioner*, 177: 619, 1956.
6. Clark, A. N. G. A new evacuant suppository. *Brit. M. J.*, 2: 866, 1957.
7. Sokolow, J. Preliminary report on the clinical use of a new laxative. *Clin. Med.*, 5: 1195, 1958.
8. Schmidt, L.: Pharmakologie und Toxikologie einer neuen Klasse von Verbindungen mit laxierender Wirkung. *Arzneimibtel-Forsch.*, 3: 19, 1953.
9. Kremer, K. and Grewe, H. E. Untersuchungen über die medikamentoese Beeinflussung der Darmperistaltik. *Ärztl. Wchnschr.*, 10:5 29, 1955.
10. Greiner, T., Bross I., and Gold, H. A method for evaluation of laxative habits in human subjects. *J. Chron. Dis.*, 6: 244, 1957.

Diagnostic Shelf

Relative vs. Organic Mitral Insufficiency

A. A. Luisada, M.D., F.A.C.C. *and* J. Szatkowski, M.D.

Chicago, Illinois

HISTORY

A fifty-four year old white woman (K. B), was admitted to the hospital in June 1958 because of sudden onset of palpitation and a sharp substernal pain radiating to both shoulders, lasting thirty minutes. Fifteen years before the patient had been told that she had an enlarged heart and she had been taking digitalis for the past three years. She stated that she had been suffering from hypertension but was rather vague about time, duration and level of blood pressure.

PHYSICAL EXAMINATION

The patient was an obese woman, who was in acute distress when first seen in the emergency room. The pulse was 180 and regular; the blood pressure was 130/80 mm. Hg. There were moist rales in the bases of both lungs, marked peripheral edema and the veins of the neck were engorged. The thyroid was enlarged.

The heart was enlarged to the left, with the apical impulse in the fifth intercostal space at the anterior axillary line. A grade 3 systolic murmur was heard along the sternal border and at the apex. The liver was palpated 3 to 4 fingerbreadths below the costal margin. The next day the heart rate was 80.

HOSPITAL COURSE

The patient was maintained on digoxin, low salt diet and chlorothiazide; on this regimen she lost at least 20 pounds. Except for an occasional episode of pain in the chest, alleviated by sublingual nitroglycerine, she was quite comfortable. On the twelfth hospital day, the patient underwent left and right heart catheterization without complications, and was discharged two days later.

ELECTROCARDIOGRAM

The record showed sinus tachycardia at a rate of 120 per minute and a P-R interval of 0.19 second. Flat to inverted T waves were present in leads I, aVL, V_5 and V_6. Notched P waves were found in leads I, III, aVR and aVL.

X-RAY FILM OF THE CHEST

This revealed marked enlargement of the heart to the right and left, enlargement of the left atrium and moderate hilar congestion.

SECOND ADMISSION

The patient was readmitted to the hospital four days after discharge because of severe sharp substernal and subcostal shooting pain in the chest associated with severe dyspnea, orthopnea and vomiting.

Physical Examination: The patient was in acute respiratory distress and there were basilar rales and distention of the veins of the neck. Temperature was 100°F.; blood pressure was 190/150 mm. Hg; and apical rate was 150 and regular. The following day the apical rate decreased to 96, but became irregular and an electrocardiogram revealed atrial fibrillation.

Hospital Course: Treatment consisted of oxygen, administration of quinidine until the rhythm was converted (twenty-four hours), and administration of heparin and digitalis.

Laboratory Data: Hemoglobin was 13.65 gm., the white blood cell count was 10,550, GOT was 27 (the next day it was 41) and the GPT was 19 (the next day it was 24).

Electrocardiogram: On admission the electrocardiogram revealed atrial fibrillation with ventricular extrasystoles; rate 140. Nonspecific S-T and T changes were present in leads I, II, aVL, aVF and V_4 through V_6.

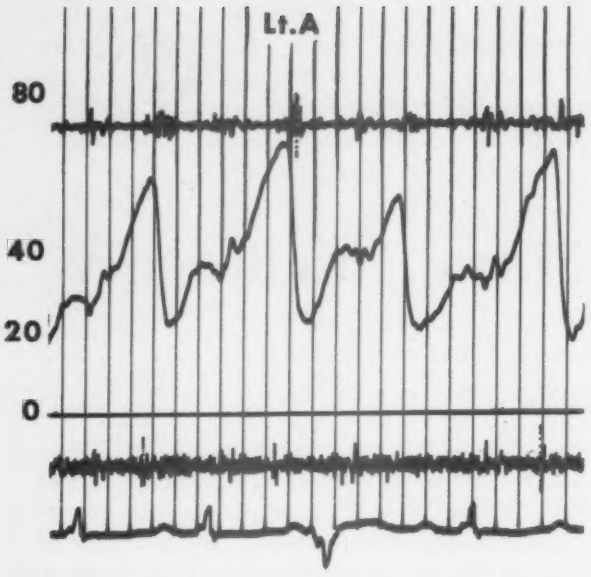


FIG. 1. Left atrial pressure curve recorded simultaneously with phonocardiograms and electrocardiogram. The left atrial pressure curve shows a high diastolic level; high, late systolic, triangular wave of insufficiency (I wave) with peak slightly before the second sound. This wave reaches a level of 60 to 70 mm. Hg.

Phonocardiogram: This revealed a slightly delayed first sound, systolic murmur in decrescendo and a large third sound at the apex.

In spite of clinical improvement, the patient died suddenly on the fourth hospital day.

COMMENTS

During the first admission, diagnosis was uncertain. The long history of cardiac enlargement and digitalization, and the vague electrocardiographic changes could be explained as due to either rheumatic heart disease or recurrent myocarditis. The history of hypertension was questioned. Coronary heart disease was doubted because of the long duration of the illness, the sex and age, the atypical changes in the electrocardiogram and the fact that precordial pain coincided with episodes of supraventricular tachycardia.

CATHETERIZATION FINDINGS

For the aforementioned reasons, cardiac catheterization was performed. Right heart catheterization revealed a right ventricular pressure of 65/7–15 mm. Hg and a pulmonary arterial pressure of 65/28 mm. Hg, i.e., severe pulmonary hypertension. Right atrial pressure was 13.5 mm.

Left heart catheterization revealed a mean pressure of 28 mm. in the left atrium. A high I (insufficiency) wave was present in the left atrium during late systole, reaching a level of 60 to 70 mm. Hg (Fig. 1). The diastolic pressure of the atrium was 27.5. The left ventricle was not entered.

It was concluded that the patient had mitral insufficiency and that the high level of the atrial pressure was probably due to left ventricular failure. The possibility of an old rheumatic lesion of the mitral valve was discussed, but no definite conclusion was reached.

AUTOPSY FINDINGS

Autopsy disclosed: (1) Severe hypertrophy and dilatation of the left ventricle, and hypertrophy of the right ventricle; (2) no valvular lesions; (3) two apical infarcts, one of them recent; and (4) arteriosclerotic narrowing of the descending branch of the left coronary artery but no occlusion.

It is evident that mitral regurgitation was relative and it is interesting to note that the pattern of the left atrial pulse was similar to that caused by organic mitral insufficiency: high regurgitant wave during ventricular systole (high I wave, also erroneously called high V wave).

Case Reports

Precipitation of Myocardial Infarction by Postural Hypotension*

FRITZ MAINZER, M.D., F.A.C.C.
Alexandria, Egypt

IN THE PRESENCE of coronary disease, myocardial infarction may be precipitated by various factors. Physiologically, all conditions which increase the discrepancy between myocardial irrigation and metabolism, or the coagulability of the blood, or both, may favor this outcome; but the clinical importance of these influences is yet highly controversial.[1,4,5]

Physical strain, mental stress, exposure to low temperature, gastrointestinal disturbances, gallbladder disease, indirect trauma to the heart (heart concussion[2]), surgical and hemorrhagic shock, infection, severe anemia, drugs enhancing the coagulation of the blood (cortisone), have been noted as precipitating factors of myocardial infarction. Several of these may be associated in the same case as will be illustrated subsequently.

It is not intended, however, to discuss here all the known precipitating factors referred to in the extensive pertinent literature. The purpose of the present paper is limited to the recording of a precipitating mechanism not yet reported hitherto, namely, postural hypotension.

For several years we have been engaged in the study of postural hypotension; we found that its occurrence is more frequent in elderly people with arteriosclerotic and/or hypertensive cerebral damage than has been realized, because in the majority of cases the disorder remains asymptomatic.[3] Thus, postural hypotension as a physiologic disturbance should be strictly distinguished from the clinical syndrome.

Since a sudden fall of blood pressure produced by surgical or hemorrhagic shock or following spinal anesthesia is a well known mechanism of myocardial infarction in patients with pre-existing coronary disease, such an association in postural hypotension can be readily conceived. The three following case histories may illustrate this event.

CASE REPORTS

CASE 1. S. S., a seventy-six year old man of slim asthenic body build, had suffered from occasional anginal attacks after effort since 1947, also after prolonged standing. A loud high-pitched holosystolic murmur was present over the whole precordial area. The heart was moderately enlarged to the left. The electrocardiogram showed minor alterations of the S-T segment which became more marked in the following years. Arterial blood pressure was between 170/70 and 145/55 mm. Hg; there was a Corrigan pulse.

Beginning 1957 his condition had become progressively worse; the anginal attacks precipitated by standing became more frequent. However, they continued to be of short duration, and were relieved by sitting down, and by the administration of nitroglycerin. Parallel with the clinical progression, the electrocardiogram (February 11, 1957) showed considerable accentuation of the abnormal features: in the six limb leads T was now isoelectric, in Nehb's lead D and in lead V_6 it became negative following a depressed S-T segment. The outstanding peculiarities of the tracing, however, were the tall (up to 9 mm.), pointed, symmetrical T waves in Nehb's leads A and J as well as in leads V_1 to V_4. Furthermore, there was a notched QS complex in leads V_1 to V_3 followed by an elevated S-T segment. This tracing was interpreted as suggestive of diffuse subendocardial ischemia associated with residual alterations from an old anterior wall infarction. The ballistocardiogram was also highly abnormal: completely irregular low-voltage deflections (grade 4 abnormality according to Brown-DeLalla). In the next tracing (February 24, 1957), recorded after a severe attack, the T waves

* From the Swiss Hospital, Alexandria, Egypt, United Arab Republic.

had become even taller (up to 12 mm.) and more pointed; the S-T depression and the negativity of T in Nehb's lead D were more conspicuous.

During 1957 three severe paroxysms occurred manifested by attacks of postural hypotension associated with severe and protracted anginal pain. On the first occasion the patient was standing rather motionless in his office for nearly a quarter of an hour discussing current business; suddenly he became dizzy with a feeling of fainting: this was followed by heavy retrosternal oppression, which lasted for half an hour after lying down. At this moment arterial pressure was 110/60 mm. Hg. Some weeks later the patient experienced a similar episode when hastily arising in the night for urination. This time, however, the cerebral manifestations were more severe; dizziness and intense anginal pain passed off only after several hours. The next morning the blood pressure was reduced to 115/60 mm. Hg and reached its usual level only later in the day. An identical attack of minor severity occurred during the summer of 1957.

Repeated tests for postural hypotension showed a fall in blood pressure from 145/65 in the horizontal position to 105/60 standing, a change unaccompanied by any symptoms. From this latter circumstance one may conclude that during these attacks the hypotension had been more severe.

In March 1958 the patient contracted a minor infection of the respiratory tract. After some days the temperature rose to 38.4° C (oral), enforcing bedrest. The next morning the fever was unchanged and the pulse rate was 100/minute. When rising from bed to go to the lavatory, the patient had a severe fainting attack with disappearance of radial pulse, loss of consciousness which lasted nearly ten minutes, extreme pallor and cold perspiration. After awakening he complained of agonizing retrosternal pain, spreading to the interscapular region, with oppression and respiratory distress. The pulse was about 140 per minute and irregular. The blood pressure was 110/50, and the heart sounds were not perceptible. After a few minutes pulmonary congestion developed. The coronary shock was resistant to treatment despite the intravenous administration of high doses of noradrenaline (Levophed®). With progressive fall of blood pressure and increasing pulmonary congestion, death occurred thirty-six hours after onset.

Comment: An old man with severe coronary disease was suffering simultaneously from postural hypotension verified by repeated tests. In the later stages of the disease this disorder gave rise to attacks of coronary insufficiency. After prolonged standing the patient initially experienced short bouts of anginal pain, which were immediately relieved when sitting or lying down. Later, as the coronary disease grew more severe, he had severe attacks of coronary insufficiency (intermediate syndrome) of long duration associated with serious cerebral manifestations of the postural circulatory disturbance. Finally, a fatal episode of myocardial infarction was precipitated under identical conditions by postural hypotension, enhanced (in accordance with pertinent experience) by the existing fever; the stress imposed on the heart by febrile infection and the influence of the infectious disease on blood coagulation may have been associated factors. During the last years of the illness postural hypotension was actually the main mechanism precipitating anginal attacks, effort being of minor importance, since the patient was careful to avoid it.

TABLE I

Blood Pressure Values in Case 2 in Orthostasis and After Resumption of Horizontal Posture (mm. Hg)

Horizontal Posture	Orthostasis	After Resumption of Horizontal Posture
195/65 190/60	150/80	230/60 180/55

Case 2. A. P., a seventy-six year old widow, had remained chronically ill following an attack of atypical bronchopneumonia in 1944. Her cardiovascular state was highly abnormal. For several years arteriosclerotic arterial hypertension with high pulse pressure (benign systolic hyptertension) and Corrigan pulse had been noted; the blood pressure approximated a level of 180/60 mm. Hg. In seven tests, performed during a period of several months, postural hypotension had been found consistently present. It was associated with marked postorthostatic hypertension,[3] a phenomenon, due to overshooting of the regulatory mechanism. Table I summarizes one illustrative test.

After standing for a short time premonitory symptoms of fainting always occurred. Twice during 1956 she had had attacks of paroxysmal tachycardia during defecation, once with subsequent fainting.

An electrocardiogram (November 29, 1956) showed the following abnormalities: isoelectric T in standard unipolar limb leads and in Nehb's leads D and A; rS complex of low voltage (3 mm.) in Nehb's lead J followed by a diphasic (+ −) T; small (2 mm.) QS deflections with negative T in leads V_1, V_2 and V_3; small R deflections (1.5 to 3 mm.) with isoelectric T in leads V_4, V_5 and V_6. The electrocardiographic diagnosis was diffuse coronary disease with old anterior wall infarction.

During October 1957, in the early morning hours,

the patient regularly had for two weeks attacks of cardiac asthma with retrosternal pain, continuously increasing in duration and intensity to a final dramatic episode which lasted several hours; this was followed by subfebrile temperatures and a progressive fall of blood pressure, from 190 to 110 mm. systolic and then to 125/55. Electrocardiographic changes resulting from this infarction (November 11, 1957) were not typical of focal necrosis, but showed rather an accentuation of the preexisting diffuse alterations. After several months the blood pressure again reached its initial level of 160/60 mm. Hg.

In February 1958 the patient had a mild infection of the respiratory tract. The temperature of 38.4° C. lasted only one morning and subsided after a few hours during the afternoon. When the patient rose from bed in the evening she fainted and lost consciousness, and her pulse disappeared for several minutes. After regaining consciousness she complained of palpitations and retrosternal oppression. The pulse rate was 140 and regular, and for one month did not slow below 100. The blood pressure in the following night was between 90/50 and 110/60 and remained below 120 mm. Hg for several weeks. There was a second elevation of temperature to 38° C. For more than a week the patient was in critical state with signs of forward heart failure. The electrocardiogram (February 12, 1958) again showed pronounced exacerbation of pre-existing alterations, but was not diagnostic of focal necrosis.

Comment: An old debilitated woman in bad general health had severe coronary disease which had given rise to bouts of paroxysmal tachycardia and to a period of cardiac asthma attacks culminating in an episode of myocardial infarction. For several years she was also suffering from postural hypotension with pronounced overshooting of arterial pressure when lying down again (postorthostatic hypertension[3]); this disorder of blood pressure regulation was clinically manifest by dizziness and palpitations when standing.

Following normalization of temperature after a febrile infection of short duration she suffered a hypotensive attack of uncommon severity when rising from bed; it precipitated a second episode of cardiac infarction.

CASE 3. I. C., a seventy-two year old widow, had for many years chronic enterocolitis with elevated sedimentation rates (40 to 100 mm. Westergren). For almost ten years she was also suffering from unstable arterial hypertension. Blood pressure varied between 145/80 and 210/110 mm. Hg. There were signs of hypertensive cardiopathy with coronary insufficiency. In 1955 mild heart failure became manifest with dyspnea on slight exertion and tendency to edema.

Since 1954 a systolic murmur was heard over the mitral area. A twelve lead electrocardiogram showed left axis deviation and very flat T waves. In October 1957 severe indigestion after a heavy evening meal was complicated by marked retrosternal oppression lasting the whole night. This was followed by fall in the blood pressure from 190/80 to 155/70 and elevation of temperature to 37.5° C. (oral) for two days. An eighteen lead electrocardiogram, taken four days later (November 4, 1957), showed alterations suggestive of posterior wall infarction: rSr′ with high takeoff of a dome-shaped S-T and symmetrical negative T in lead III; QR of low voltage (1.8 mm.) with isoelectric T in aVF. In a subsequent tracing (November 27, 1957) the typical alterations were more marked: QS (7 mm. voltage) with dome-shaped S-T taking off isoelectrically and negative symmetrical T in lead III; same contour with lower voltage (3 mm.) of the main complex in aVF. By this time further changes had appeared in other leads suggesting extension of the lesion to the anterior wall. A QS complex appeared in leads V_1 and V_2 followed by a dome-shaped S-T; T became negative in leads V_1 to V_6 and in lead J (Nehb). The convalescence was uneventful.

From January 19 to 21, 1958, the patient had a febrile respiratory infection. During the night of the third day the temperature dropped from 39.5° to 36.8° C. In the morning the patient obsessed, as she was always, by the idea of constipation insisted on having an enema and then rose from bed to go to the lavatory. On rising, she had a spell of severe dizziness; at the moment of evacuation she fainted and fell to the floor. Unconsciousness may have lasted ten minutes. When she awakened she complained only of weakness. Half an hour later systolic blood pressure was 80 mm., diastolic was not yet measurable; the next day the blood pressure was 110/55. There was another brief temperature elevation to 37.5° C. During the following days the heart sounds became progressively dull, the systolic murmur faded away completely and marked bilateral pulmonary congestion appeared; two weeks later the manifestations of heart failure began to regress slowly.

The first electrocardiographic tracing taken after the fainting episode (January 15, 1958) showed the appearance of left bundle branch block which, however, was regularly absent in the systoles which followed numerous ventricular premature beats and their compensatory pause (intermittent left bundle branch block). In a subsequent electrocardiogram (February 6, 1958) the block was intermittent even in the absence of premature beats; but in leads III and aVF and later also in lead II the contours of a recent posterior wall infarction appeared again, masked once more in a later tracing (March 3, 1958) by left bundle branch block.

After convalescence the patient complained of fainting attacks when rising from bed in the morning. Repeated tests showed the permanent presence in

these circumstances of postural hypotension with blood pressure levels of 145/70 to 130/60 in the supine position falling to 100/70 to 95/60 in orthostasis. This is circumstantial evidence, although no definite proof of the pre-existence of this disorder before the infarction.

Comment: An elderly woman with labile high blood pressure and coronary disease had a first myocardial infarction following an acute indigestion. Eleven weeks later, while recovering from a febrile respiratory infection, she experienced a severe prolonged attack of postural hypotension with fainting, when she arose from bed and was evacuating an enema. This episode was followed by immediate evidence of a second painless posterior wall infarction with subfebrile temperatures, fall of blood-pressure, transient left heart failure and diagnostic electrocardiographic findings. After recovery the presence of permanent postural hypotension, presumably pre-existent, was ascertained by repeated tests and gave rise to clinical manifestations.

Comments

The three cases reported are instances of myocardial infarction precipitated by postural hypotension. The direct observation of this causal relationship is impossible for obvious reasons because there can be no opportunity to measure blood pressure in orthostasis just before the onset of infarction. But there is the strongest circumstantial evidence based on the following arguments:

(1) In all three cases the infarction set in at the very moment of the rising from bed and was associated with severe cerebral manifestations of hypotension; on the other hand, simultaneous cardiac manifestations were absent in two patients.

(2) In all three cases postural hypotension was permanently present as shown by repeated tests in two patients before infarction, and in the third one after recovery from the attack. In two patients spells of postural hypotension had been observed before the infarction and had given rise to previous cerebral and cardiac manifestations.

(3) A serious disturbance of cardiac rhythm as a possible cause of arterial hypotension was present only in the first patient during his fatal attack. This patient, however, had previously had four other episodes of postural hypotension with severe cerebral and cardiac manifestations, but with normal rhythm.

Accidental factors enhancing the permanent tendency to postural hypotension were present and may have conditioned the fall of blood pressure beyond the limit of catastrophe; fever was present or just abating in all three cases. This effect of the febrile state as well as that of high environmental temperature is due to the well known competition between antagonistic circulatory regulations taking place in these circumstances, vasoconstriction as a means of maintaining blood pressure in orthostasis and vasodilation as a tool of temperature regulation. In the third patient another factor enhancing hypotension was the suction effect on the blood due to the sudden release of abdominal pressure by the evacuation of an enema.

With the present case histories postural hypotension comes to be established as a new factor which may precipitate myocardial infarction in patients with pre-existing coronary disease. Since this disorder is by far more common than has been realized until now,[3] its role may become more important if searched for in every pertinent case.

Summary

The histories of three patients with progressive coronary disease are reported in which an attack of myocardial infarction, fatal in one instance, was precipitated by an episode of preexisting permanent postural hypotension. Accidental factors enhancing the tendency to arterial hypotension were operative in every case; a febrile (or postfebrile) state in all three cases and in one a sudden release of abdominal pressure. In view of the frequency of asymptomatic postural hypotension, not fully realized hitherto, such cases are expected to be met in increasing numbers.

References

1. Master, A. M., Dack, S. and Jaffe, H. L. Factors and events associated with onset of coronary artery thrombosis. *J.A.M.A.*, 109: 546, 1938.
2. Mainzer, F. Heart contusion in coronary disease. *Cardiologia*, 16: 288, 1950.
3. Mainzer, F. Orthostatischer Blutdruckabfall im Gefolge des Schlaganfalls und bei cerebraler Arteriosklerose; Postorthostatische und orthostatische Hypertonie. *Nervenarzt.*, 29: 337, 1958.
4. Paterson, J. C. Relation of physical exertion and emotion to precipitation of coronary thrombi. *J.A.M.A.*, 112: 895, 1938.
5. Paterson, J. C. Capillary rupture with intimal hemorrhage as causative factor in coronary thrombosis. *Arch. Path.*, 25: 474, 1938.

Localized Pulmonary Fluid Collections in Congestive Failure Simulating Tumors

Phantom Tumors of the Lung*

ISIDORE STEIN, M.D., F.A.C.C. *and* JOSEPH WEINSTEIN, M.D., F.A.C.C.

Brooklyn, New York

SINCE the original description by Stewart,[1] the subject of vanishing tumors of the lung has intrigued not only cardiologists but also lung specialists as well as chest surgeons. The possibility of a pulmonary neoplasm poses the problem of differential diagnosis, which may often be established by intensive cardiac therapy. These x-ray shadows are usually located on the right side[2] between the upper and middle lobes, but occasionally they may appear in the oblique interlobar fissure. They vary in shape[3] and may be round, spindle, semilunar, bridge or linear but are most often ovoid or elliptical. The configuration depends on the nature of the fluid, its position, the angle of projection of the roentgenogram and the amount of surrounding pulmonary compression.

In this modern era of thoracic surgery with the tendency to early exploration, it is of vital importance to differentiate these localized chest shadows from pulmonary tuberculosis, pneumonia, neoplasm or lung infarction. With this in mind it was thought worthwhile to report the following cases.

CASE REPORTS

CASE 1. H. B., a forty-seven year old white man, suffered an attack of acute myocardial infarction in 1954, from which he made a good recovery. Two years later chest pain developed with radiation to the left arm and increasing shortness of breath on walking, relieved by rest. There were no other symptoms referable to the cardiovascular system. Neither the patient nor his family ever had diabetes or hypertension.

Clinical Findings: The physical examination revealed a well developed man, in no acute distress, who weighed 175 pounds. Blood pressure was 104/90 mm. Hg. There was no orthopnea. The heart was enlarged to the left; sounds were of fair quality, the second aortic being louder than the second pulmonic sound; rhythm was regular. A grade 3 systolic murmur was audible at the apex and in the left axilla. There were scattered medium rales posteriorly in both lung fields. The liver was not palpable nor was there any edema. The aforementioned signs were indicative of left heart failure.

Urinalysis revealed 2 plus albumin; the red blood cell sedimentation was 20 mm. in one hour. The electrocardiogram revealed evidence of an old posterolateral wall infarction and left bundle branch block.

Roentgenographic studies of the chest (Fig. 1) indicated left ventricular enlargement and moderate pulmonary congestion especially on the right side. Oval-shaped and discretely outlined masses were present in the horizontal fissure laterally and in the posterior portion of the oblique fissure. There was no free pleural fluid.

Clinical Course after Treatment: The patient was placed on modified bedrest, and given a low sodium diet, digitalis and mercurials. Two days later he felt only slightly better but the shadows had begun to shrink. The inferior aspect of the right horizontal fissure had the appearance of a flat teardrop (Fig. 2). Five days after the beginning of treatment a thin line of fluid was visible in the short fissure (Fig. 3). Two weeks later the chest film showed no evidence of fluid. Although the lungs remained clear, pretibial edema subsequently developed which disappeared following more intensive mercurial administration.

He was symptom-free for about a month, when he suddenly slumped to the floor and died.

Postmortem Findings: The autopsy report was acute cardiac failure due to occlusive coronary disease involving the right and left coronary arteries. The heart weighed 490 gm. The right auricle and ventricle, as well as the left auricle, were markedly dilated. The left ventricular myocardium measured 0.8 to 1 cm. in thickness. Its subendocardial surface

* From the Department of Medicine, Jewish Hospital and New York State University College of Medicine, Brooklyn, New York.

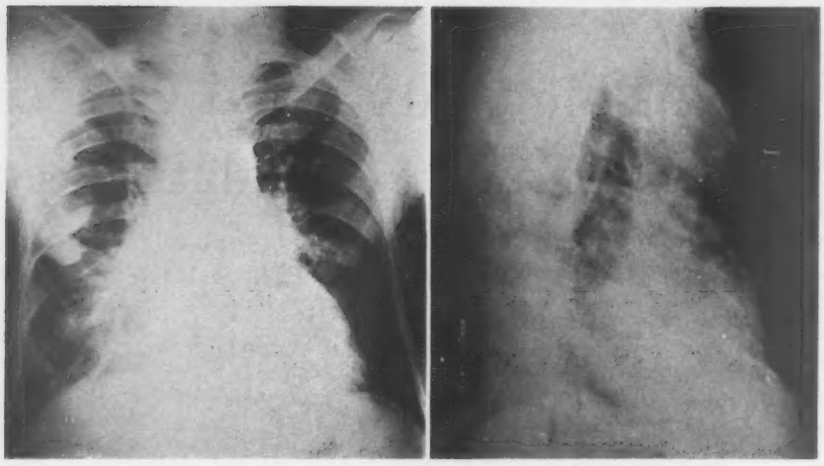


FIG. 1. Case 1. Posteroanterior and lateral roentgenograms before treatment.

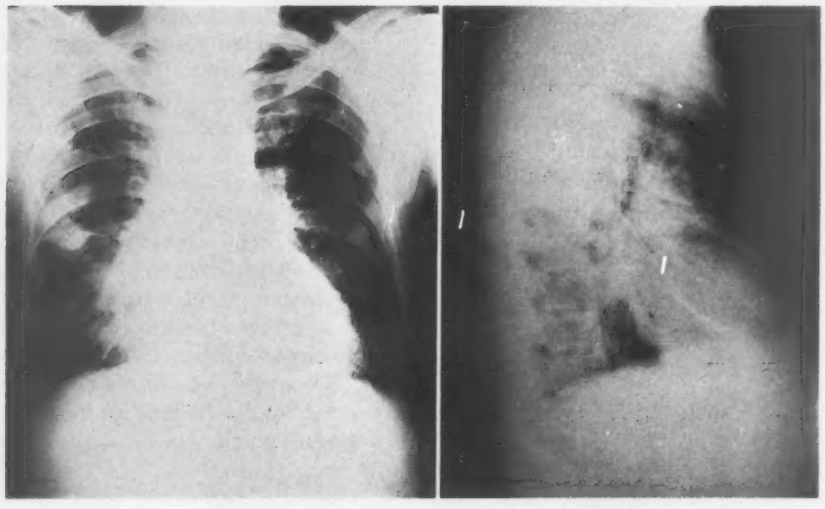


FIG. 2. Case 1. Roentgenograms two days after treatment for congestive failure.

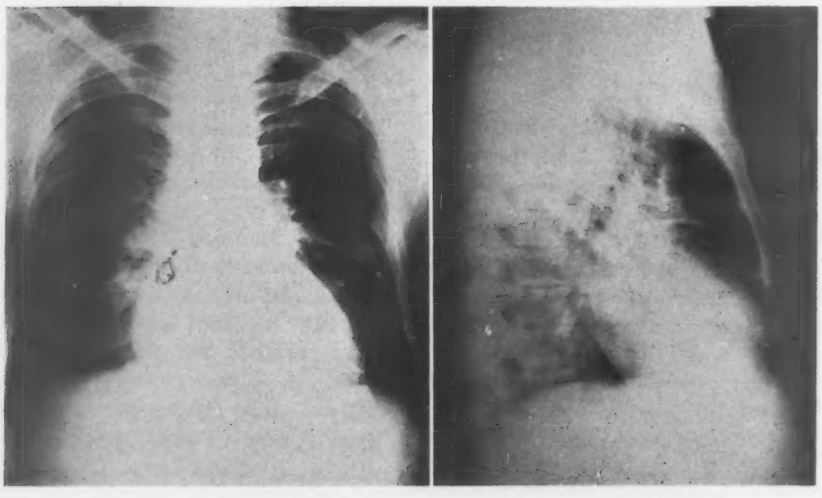


FIG. 3. Case 1. Roentgenograms five days after treatment.

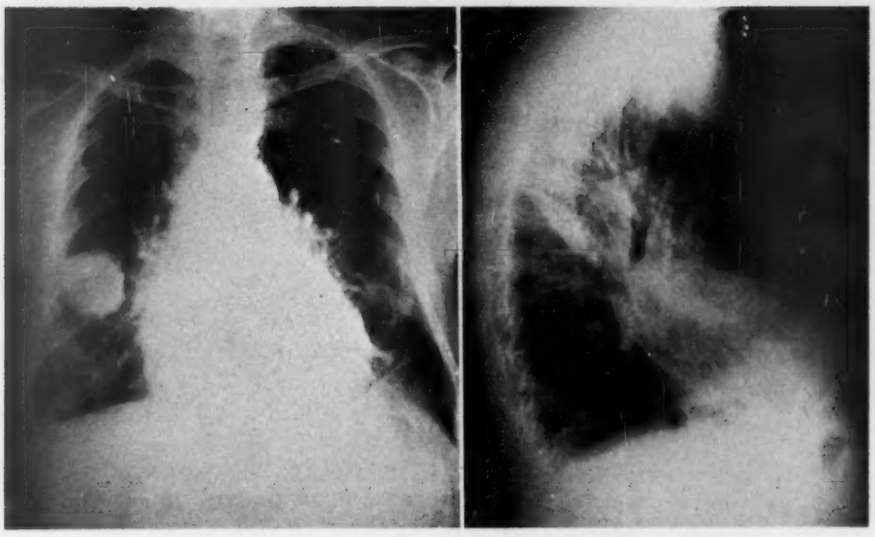


FIG. 4. Case 2. Roentgenograms before treatment (January 31, 1955).

revealed areas of marked thickening. The coronary arteries showed extensive atheromatous degeneration. There was an old, white, noncalcific occlusion just beyond the orifice of the left coronary artery. In the right coronary artery, about 3 cm. from the orifice, was an old occlusion. The remainder of the coronary vessels were narrowed to about 50 per cent of their normal diameter. Sections of the myocardium revealed extensive fibrous replacement.

Sections of both lungs showed congestion and edema throughout. The pleural surfaces were smooth and glistening. The liver, spleen and kidneys were also congested.

There were no adhesions or fluid in the pleural cavities. Congestion and edema were present on sectioning both lungs.

CASE 2. L. L., a seventy year old clothing cutter, complained of lower abdominal pain beginning seven months prior to admission. This was accompanied by nausea, anorexia, occasional diarrhea and a loss of 15 pounds in weight. There were no tarry stools and no symptoms relating directly to the heart.

Clinical Findings: Examination revealed a well developed, well nourished and not acutely ill man. Temperature was 100.8°F. and weight 178 pounds. Blood pressure was 160/90 mm. Hg. The heart was enlarged slightly to the right and left. The lungs were clear. The abdomen was distended and tenderness was noted in the left groin. Bilateral pretibial edema (1 plus) was present. The prostate gland was hard and enlarged (3 plus).

Laboratory studies disclosed: hemoglobin, 9 gm. per cent, red blood cells 2,050,000 per cu. mm., white blood count 9,500 per cu. mm. with a normal differential. Urine was normal except for 1 plus albumin; urea nitrogen, 50 mg. per cent; creatinine, 2.7 mg. per cent; acid phosphatase, 5 units (Gutman). The sedimentation rate was 25 mm. in one hour.

The teleroentgenogram* on January 31, 1955 (Fig. 4), disclosed marked cardiac enlargement especially to the left, left pleural adhesions, fibrous pleuritis (right) and a large rounded mass of discretely outlined density overlying the right horizontal fissure. There was moderate pulmonary congestion and no significant amount of free fluid.

The electrocardiogram on January 30 indicated atrial flutter with a ventricular rate of about 150/minute.

Clinical Course after Treatment: The patient was placed on a low sodium regimen, and given digoxin and mercurial injections, in addition to 250 cc. of packed red cells. This resulted in moderate improvement; the edema disappeared and ventricular rate slowed to 82/minute. The patient felt stronger although he continued to complain of pain in the pelvic and scrotal areas. He again received 250 cc. of packed cells six days later. On February 10 the hemoglobin was 12 gm. per cent and the red blood cell count was 3,890,000 per cu. mm.

The urological consultant suggested administration of stilbestrol, 10 mg. three times a day, and radiation therapy to the anterior pelvis. He received treatment on two consecutive days for a total of 400 r.

Fluoroscopy of the chest on February 5 (five days after the institution of therapy) still showed a small amount of fluid in the right horizontal interlobar fissure.

On February 14 the rounded mass in the right midthorax had disappeared (Fig. 5). There was no fluid on either side but a minimal degree of pulmonary congestion was evident.

The electrocardiogram on February 7 revealed a regular rhythm and a rate of 82/minute with generalized flattening of the T waves.

* We are grateful to Drs. Emanuel Mendelsohn and Morris Witten for the interpretations of the x-ray films

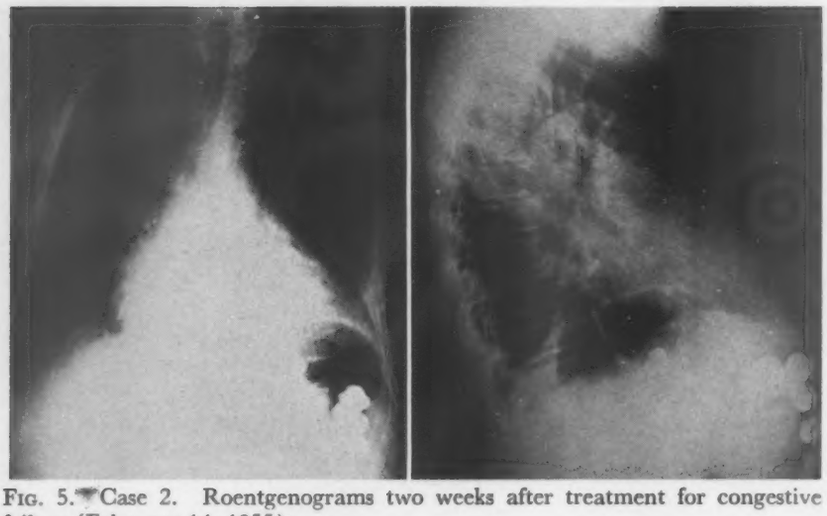


FIG. 5. Case 2. Roentgenograms two weeks after treatment for congestive failure (February 14, 1955).

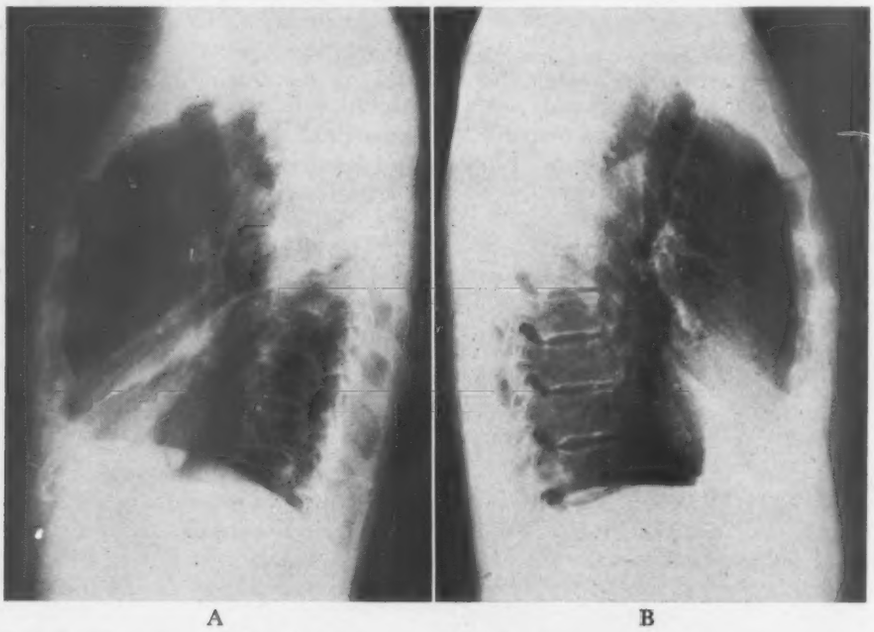
On February 15 the patient suddenly became comatose, with muscular twitching which lasted half an hour. The pulse was regular at 72/minute.

The electrocardiogram was interpreted as first degree A-V block and right bundle branch block, coronary insufficiency and possible digitalis effect. No residual neurologic signs were manifested. Seven hours later respirations increased and pulmonary edema ensued. Treatment was of no avail and he ceased breathing shortly thereafter. Permission for necropsy was not granted. The final diagnosis was pulmonary edema and carcinoma of the prostate gland.

CASE 3. J. R., a sixty-seven year old white man, complained of a productive cough for many years and shortness of breath for about two years. He was not a smoker and the past history was non-contributory except that forty years before he had worked as a hard coal miner for a period of six months.

Clinical Findings: Physical examination revealed a somewhat undernourished man weighing 126 pounds. The lungs showed no unusual findings. There was minimal left ventricular enlargement with a blood pressure of 160/98 mm. Hg. The heart rhythm was regular, and the rate 78/minute. Edema was not present nor were the liver and spleen palpable.

Sputums were negative for acid-fast bacilli. A chest roentgenogram revealed minimal left ventricular enlargement and pulmonary congestion with a shadow in the interlobar fissure of the right lung (Fig. 6A).



A B

FIG. 6. Case 3. A, lateral roentgenogram before treatment. B, roentgenogram after treatment for congestive failure.

Clinical Course: The patient was kept under observation for tuberculosis for a period of over a year with no essential change in his condition. Cardiac therapy, consisting of digitalis, mercurials and a low sodium diet was then instituted, and his condition soon improved. The pulmonary congestion and the interlobar shadow practically vanished (Fig. 6B).

Comments

The importance of prompt diagnosis of a localized pulmonary collection of fluid caused by a failing heart lies not only in the ease of treatment but in avoiding other drastic therapy as for pulmonary tuberculosis, neoplasm or infarction. This is particularly true today when early exploratory thoracotomy is recommended for localized lesions of undetermined etiology. None of the latter can be influenced by diuresis as can a localized pleural effusion due to congestive failure.

These effusions may accumulate due to an obliterative pleuritis[4-6] so that the fissures would be the only available place in which a pleural transudate could collect. Adhesions were noted in the roentgenograms of the patient in Case 2, but absent on autopsy in Case 1.

Stein and Schwedel[7] dispute this interpretation. They presented patients who failed to show any evidence of obliterative pleuritis on postmortem examination. They believed that the condition is caused by a deep congenital indentation in the region of the interlobar fissures which tends to hold the transudate formed during heart failure.

Although single effusions have been the rule, more than one localization has been reported. Roesler[8] described a patient in whom fluid was present simultaneously in the right transverse and oblique fissures. Di Maio[9] reported a case in which, in addition to a collection in the right transverse fissure, there was a localized fluid mass in the right upper lateral portion of the pleural cavity and in the anterosuperior paramediastinal space. The patient in Case 1 presented fluid collections in both the transverse and oblique fissures.

One must suspect that these "tumors" may have an underlying cardiac basis when, in addition, heart enlargement and pulmonary congestion are present. The configuration of the pulmonary shadows is often characterized by an "onion" or "tear drop" appearance with tapering at either end. The diagnosis can be definitely established by the therapeutic administration of cardiotonic drugs, particularly mercurial diuretics. The "tumor" will practically melt after several days of such medication.

Summary

Three cases are reported presenting localized lung "tumors" which disappeared following treatment for congestive heart failure. The literature is reviewed and the importance of recognizing the involved etiologic factors is stressed, particularly in these days when early exploratory thoracotomy may be recommended.

References

1. Stewart, H. J. Pleural effusion localized in an interlobar space: report of a case of heart failure together with autopsy. *Am. Heart J.*, 4: 227, 1928.
2. McPeak, E. M. and Levine, S. A. The preponderance of right hydrothorax in congestive heart failure. *Ann. Int. Med.*, 25: 916, 1946.
3. Gefter, W. I., Boucot, K. R. and Marshall, E. W. Localized interlobar effusion in congestive heart failure. *Circulation*, 2: 336, 1950.
4. Feldman, D. J. Localized interlobar pleural effusion in heart failure. *J. A. M. A.*, 146: 1408, 1951.
5. Newman, W. and Jacobson, H. G. Bizarre pulmonary roentgenographic manifestations in heart disease. *Am. Heart J.*, 42: 184, 1951.
6. Weiss, W., Boucot, K. R. and Gefter, W. I. Localized interlobar effusion in congestive heart failure. *Ann. Int. Med.*, 38: 1177, 1953.
7. Stein, I. D. and Schwedel, J. B. Interlobar effusion in patients with heart disease. *Am. Heart J.*, 10: 230, 1934.
8. Roesler, H. Clinical Roentgenology of the Cardiovascular System, 2nd ed. Springfield, Ill., 1943, Charles C Thomas.
9. Di Maio, M. Multiple localized pleural effusions as a manifestation of congestive heart failure: report of a case. *New England J. Med.*, 238: 502, 1948.

Extreme Hypertrophy of the Left Atrial Appendage

The Case of the Giant Dog Ear*

EDMUNDS GREY DIMOND, M.D., F.A.C.C., C. FREDERICK KITTLE, M.D., F.A.C.C. *and* DOUGLAS W. VOTH, M.D.

Kansas City, Kansas

NUMEROUS pathologic conditions involving the atria and the atrial appendage have been described. However, we believe this to be the first reported case of a hypertrophied left atrial appendage herniated through a pericardial defect, visualized by angiocardiography and corrected by resection.

CASE REPORT

A forty-seven year old white married male livestock broker was referred to the Kansas University Medical Center for study.† During a general examination (for headache and muscle cramps), x-ray films of the chest demonstrated an elongated wedge-shaped density overlying the left border of the heart (Fig. 1A).

Electrocardiographic Findings: The admission electrocardiogram (Fig. 2) demonstrated inverted T waves in lead I and a peculiar deflection of the baseline immediately prior to the onset of the QRS. At first impression one would assume this is but part of the depolarization complex and perhaps an evidence of accelerated conduction. Study of lead aVL, however, indicates that if this deflection is considered a part of the QRS, then the total QRS duration would be 0.16 second, which seems improbable in view of the normal contour of the chest leads.

X-Ray Findings: The last previous chest x-ray films in 1956 (two years prior to admission) had not disclosed any mass along the left heart border. However, there was a suggestion of inflammatory disease in the area of the left lung adjacent to the pulmonary outflow tract.

On the preoperative chest films (Fig. 1A) the heart appeared normal in size. An unusual density extending along the left heart margin was observed to be apparently separate from the heart. It appeared to be continuous with the left hilar shadow or perhaps the thoracic aorta.

Fluoroscopic examination suggested a slight enlargement of the left ventricle. The main pulmonary artery appeared normal. Along the left heart margin an actively pulsatile mass was observed which appeared to beat synchronously with the left ventricle.

Angiocardiography via femoral vein catheterization demonstrated that the pulsatile mass filled with dye after the pulmonary vasculature and in approximately the same time as the left ventricle. It was observed to be a shadow distinct from the left atrium.

Preoperative Diagnosis: Differential diagnosis included: a thoracic aortic aneurysm, a kinked thoracic aorta simulating an aneurysm, an extremely vascular cystic tumor mass or an aneurysm of the left ventricle. The diagnosis of ventricular aneurysm was felt to be the most likely and the patient was transferred to the surgical service for exploration.

SURGICAL FINDINGS

A posterolateral approach with resection of the fifth left rib was utilized. Inspection and palpation of the lungs, ventricles and thoracic aorta revealed no abnormalities. The left atrial appendage was found lying free in the pleural cavity, anterior to the lung hilum, having herniated through a pericardial defect which was about 2.5 cm. in diameter (Fig. 1B). The appendage was approximately 11 cm. long and its wall was quite thick. Exploration of the left atrium with the forefinger did not reveal any abnormality of the mitral valve or the left ventricle. The appendage was clamped at its base and continued to beat independently for three to four minutes. Rhythmical contractions were noted for thirty to forty seconds after it was excised at its junction with the left atrium. The pericardial defect was loosely sutured. The patient tolerated the operative procedure well.

The specimen weighed 31 grams and measured

† The patient was referred to us through the courtesy of Dr. Thomas Cochran of Springfield, Missouri.

* From the Cardiovascular Laboratory and the Department of Surgery, University of Kansas Medical Center, Kansas City, Kansas.

This work was supported in part by a grant from the Kansas Heart Association and the Undergraduate Cardiovascular Teaching Grant from the National Heart Institute.

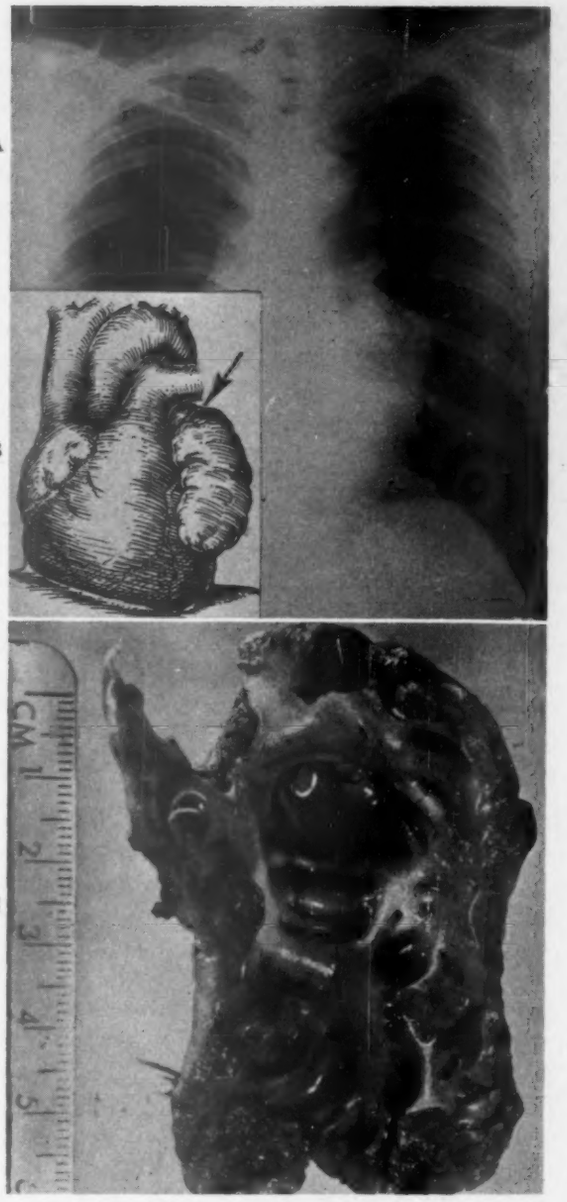


FIG. 1. A, preoperative chest film demonstrating the elongated wedge-shaped density overlying the left border of the heart. B, (inset) artist's conception of the huge left atrial appendage. C, gross specimen of the resected organ, positioned as in the ink sketch but laid open to demonstrate the marked hypertrophy.

11.0 x 3.5 x 2.5 cm. On gross inspection the epicardium, myocardium and endocardium were normal (Fig. 1C). Microscopic sections* showed hypertrophied and vacuolated myocardial fibers with variation in size and shape of nuclei. A few scattered foci of lymphocytes were seen. There was no indication of old or recent infarction and Aschoff bodies were not seen.

* Dr. James O. Boley, Department of Surgery and Pathology, University of Kansas Medical Center, very kindly reviewed the sections for us.

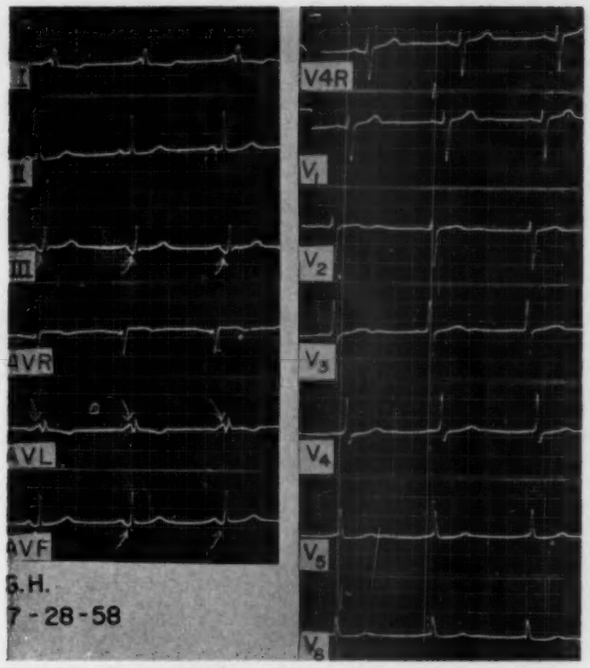


FIG. 2. Preoperative electrocardiogram demonstrating inverted T waves in leads I and aVL, and the peculiar deflection of the base line prior to ventricular depolarization, best seen in leads III, aVL and aVF.

Postoperatively, a supraventricular tachycardia with varying rates and rhythms developed. The neck veins were moderately distended, and inspiratory moist crepitant rales were audible bilaterally in both lung bases. The patient was digitalized and improved on the usual cardiac regimen. He was discharged on the twenty-fourth hospital day.

COMMENTS

Fry[1] reported a case of "herniation of the left auricle" through a defect in the pericardium. The auricle (the appendage) was noted to be "slightly larger than normal." Correction was not attempted. He considered the herniation to be due to a congenital defect in the closure of the pleuropericardial membrane.

According to Arey, "Rarely there is a faulty development of a pleuropericardial membrane which permits the cavities containing the heart and lung to communicate."[2] He refers to the condition as "incomplete pericardium." Potter[3] states: "Abnormalities of the pericardium and pericardial cavity are uncommon except when other malformations affect the mediastinum. The pericardium is seldom partially or completely absent in otherwise normal individuals." Associated defects were not observed in this case.

Very few cases of unusual malformations of the atria or their appendages have been studied.[4–8]

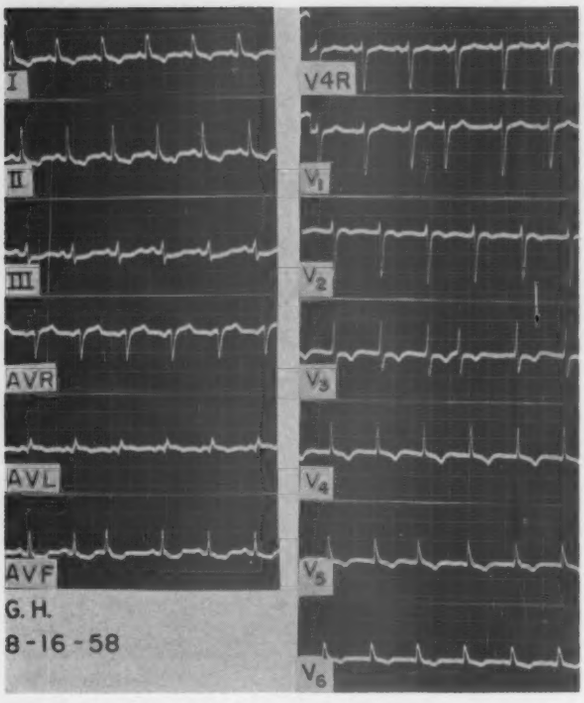


FIG. 3. Tracing taken following surgical excision of the appendage. Notice the disappearance of the P-R interval abnormalities. The RS-T and T wave changes of surgical pericarditis are noted.

Hypertrophy under various influences is well known; however, we could find no reference to hypertrophy or malformation of the left atrial appendage that was comparable to the unusual finding in this case. A history of trauma could not be elicited. Perhaps a congenital defect in the pericardium may explain the projection of the appendage into the pleural cavity. It is feasible that the enormous size of the appendage also represents a congenital anomaly, but the x-ray films of the chest taken two years before admission did not suggest such an abnormality. Myocardial infarction involving the left atrium or its appendage may result in an aneurysm of the appendage. However, in our patient the wall of the mass was thickened and hypertrophied, not thinned and dilated. There is no evidence to substantiate this concept; also this would not explain the pericardial defect.

Purely as theory, one might suggest that the defect had been present congenitally, but the appendage had become "trapped" only in recent years. The peculiar anatomic arrangement suggests the possibility that during diastole blood flows into the appendage and the actual filling acted to cut off the outflow at the "neck," with systole. One can visualize the appendage "pumping" itself into a more and more massive state.

The peculiar electrical activity of the appendage was impressive. It contracted with great vigor and its distal tip would flip in an arc of approximately 3 inches with each systole. After cross-clamping of its origin, it continued to beat and after amputation it contracted rhythmically for more than thirty seconds. In studying the preoperative electrocardiogram one is impressed by the small deflection occurring immediately in front of the QRS (particularly well demonstrated in leads III, aVL and aVF). This deflection is not part of the QRS. Note that the total duration of the QRS in lead aVL would be 0.16 second if this deflection was attributed to ventricular depolarization. All postoperative electrocardiograms indicate the greatest QRS deviation in this lead to be less than 0.10 second (Fig. 3). Again, as theory, one wonders if this strange deflection, which disappeared after amputation was not the electrical signal from this large muscle mass (31 gm.).

SUMMARY

1. We have described the case of a forty-seven year old male patient with a huge left atrial appendage herniated through a pericardial defect. This mass was 11 cm. long and was, very probably, the site of an electrical signal. Electrocardiographic evidence of this was best demonstrated by P wave and P-R interval alterations in leads III, aVL and aVF.

2. Following surgical excision, the peculiarities seen in the preoperative electrocardiogram disappeared.

3. This is the first reported instance of such an abnormality which was visualized by angiocardiography and corrected by resection.

REFERENCES

1. FRY, W. Herniation of the left auricle. *Am. J. Surg.*, 86: 736, 1953.

2. AREY, L. B. Developmental Anatomy, 6th ed., pp. 289–291. Philadelphia, 1954. W. B. Saunders Co.

3. POTTER, E. L. Pathology of the Fetus and the Newborn, p. 212. Chicago, 1952. The Year Book Publishers.

4. DANOVICH, B. Z. and PARETSKAIA, F. L. Ob anevrizme pravogo predserdiia. *Klin. med.*, 34: 78, 1956.

5. DESAI, M. G. Widened and kinked descending part

of the thoracic aorta simulating intrathoracic tumour. *Brit. J. Radiol.*, 30: 391, 1957.

6. Hayden, W. deG., Cramm, C. J., Williams, B. H. and Stinson, J. C. Invagination of left auricular appendage, resulting in sudden death. *Am. J. Dis. Child.*, 91: 287, 1956.
7. Higginson, J. and Keeley, K. J. An unusual cardiac aneurysm in a young adult. *J. Clin. Path.*, 4: 342, 1951.
8. Latour, H., Peuch, P. and Roujon, H. Coeur tri-atrial bi-auriculare gauche. Bases de diagnostic. *Arch. mal. coeur*, 51: 132, 1958.

Primary Mesothelioma of the Pericardium

JEAN L. FOREST, M.D. *and* MICHAEL C. KOZONIS, M.D., F.A.C.C.

Pontiac, Michigan

PRIMARY neoplasm of the heart is most uncommon and of the pericardium extremely rare, justifying the detailed report of a single case. Twenty-nine cases of primary pericardial tumor have been reported in the American and English literature to date.[1–13] In these cases males have been more susceptible, with a ratio of twenty-one males to eight females. The range in age is from eight to seventy-nine years with the greatest incidence in the third and fourth decade. The antemortem diagnosis was made in only two cases and was entertained as a possibility in a third.

With the more recent diagnostic tools at our command the frequency of antemortem diagnosis of this entity should increase, and the improvements in cardiac surgical technic may make operative removal of some of these tumors practical. We present the following case to call attention to this rare entity, to urge its consideration in differential diagnosis and to make some suggestions regarding the means available to establish the diagnosis.

CASE REPORT

E. S., a sixty year old obese white woman was admitted to St. Joseph Mercy Hospital on September 4, 1957, in a state of shock, associated with sudden severe pain in the upper right side of the abdomen, vomiting and dyspnea. The past history was noncontributory except for previous essential hypertension and a duodenal ulcer.

Examination revealed a systolic blood pressure of 80 mm. Hg and a regular heart rate of 100 per minute. The heart was moderately enlarged and the heart sounds were distant. No murmurs were audible and the remainder of the physical examination was within normal limits. The clinical impression was probable acute myocardial infarction. Laboratory studies revealed a normal white blood count and differential, serum amylase and transaminase, and 2-plus proteinuria. Moderate cardiomegaly was confirmed by a roentgenogram of the chest. An electrocardiogram revealed uniform low voltage and non-specific T wave inversion in leads II, III and aVF and in the left precordial leads.

The patient improved after administration of Wyamine® sulfate, oxygen and Demerol.® A grade 3 apical systolic murmur was heard on the day following admission and 3-plus edema of the ankles was present.

The patient continued to improve on bed rest, a low sodium diet, digitalis and diuretic therapy. On the fifth hospital day severe distress in the right upper quadrant developed again. Fullness and tenderness were present in the right upper quadrant and moist inspiratory rales were heard at the right base posteriorly. An upper gastrointestinal series revealed no abnormalities; a cholecystogram showed a non-functioning gallbladder with calcific densities in the area of the gallbladder.

On the thirtieth hospital day a cholecystectomy was performed, although a pericardial friction rub was recorded by one examiner prior to surgery. Cardiac cirrhosis was noted at laparotomy. Despite the therapeutic program described, two-pillow orthopnea persisted postoperatively associated with moderate distention of the cervical veins and 6 cm. hepatomegaly. The pulse pressure remained within normal limits.

The patient was readmitted on November 12, 1957. One week prior to the second admission nausea, diarrhea and pain in the left upper quadrant developed. Exertional dyspnea and marked asthenia accompanied this episode. On the day of admission the patient had severe left pleuritic pain and two-pillow orthopnea. The blood pressure was 120/80 mm. Hg with a regular heart rate of 90 per minute. Moist inspiratory rales and diminution of breath sounds were noted at the left base posteriorly, with gross cardiomegaly and distant heart sounds (Fig. 1). Moderate tenderness was present in the left upper quadrant. There was hepatomegaly, distention of the cervical veins and 2-plus pitting edema of both lower extremities with a deep thrombophlebitis on the right.

Anticoagulant therapy, a strict low sodium diet and diuretic program was instituted immediately. Maintenance therapy with digitalis was continued. A repeat electrocardiogram showed persistent inversion of the T wave in leads II, III, aVF and V_4 through V_6 (Fig. 2). Further diminution of R waves was noted throughout the tracing. Fluoroscopy of the chest revealed a grossly enlarged heart compatible with pericardial effusion. There was absence of pulsation of the left border and decreased pulsation

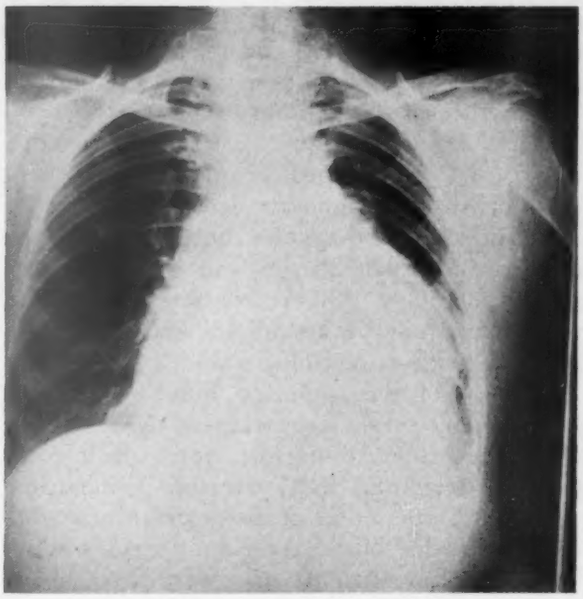


FIG. 1. Roentgenogram of the chest showing bizarre cardiomegaly.

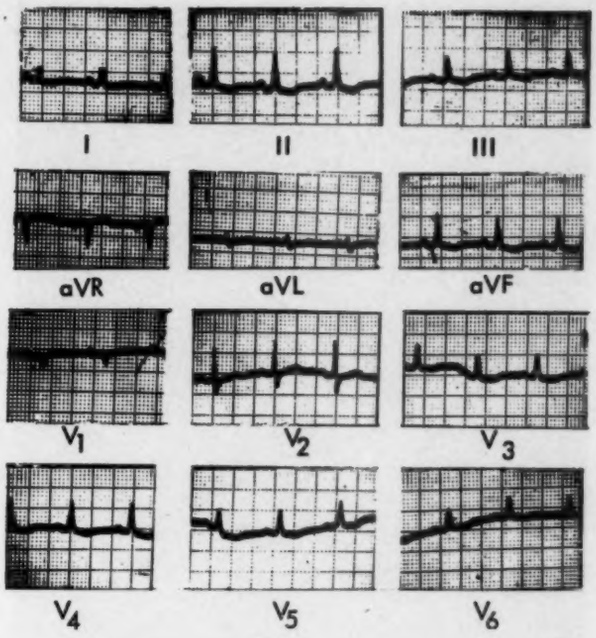


FIG. 2. Electrocardiogram taken during last hospital admission.

of the right. On the ninth hospital day the patient died suddenly before a scheduled diagnostic pericardial paracentesis.

POSTMORTEM EXAMINATION

At postmortem examination the heart and pericardium were globular and occupied most of the anterior thorax, extending from the right midclavicular line to the left anterior axillary line, compressing the aorta and underlying structures. There was no pleural effusion.

The pericardial cavity was obliterated by neoplasm with many loculi of bloody fluid, each containing not more than 5 or 6 cc. The neoplasm was soft and encephaloid, arose in the posterior pericardium and extended in all directions, embracing the heart. It involved the inner surface but did not extend through the parietal pericardium. There was no gross evidence of invasion of the myocardium but there was extension along the pulmonary vessels. The heart and pericardium together weighed 1,310 gm. The coronary arteries showed marked atherosclerosis with narrowing of the lumen, but no evidence of old or recent myocardial infarction.

Microscopic examination of the tumor revealed two distinct types of tissue. The predominant pattern was that of strands and whorls of spindle cells (Fig. 3); interspersed were less dense areas containing clefts, lined by plump epithelial cells (Fig. 4). Only an occasional mitotic figure was noted. The blood spaces were of capillary type. Some of these were thrombosed and associated with large areas of necrosis and linear scars. The narrow zone of persistent epicardium showed moderate round cell infiltration but no microscopic evidence of invasion of the myocardium by tumor. There was extension of the tumor along the

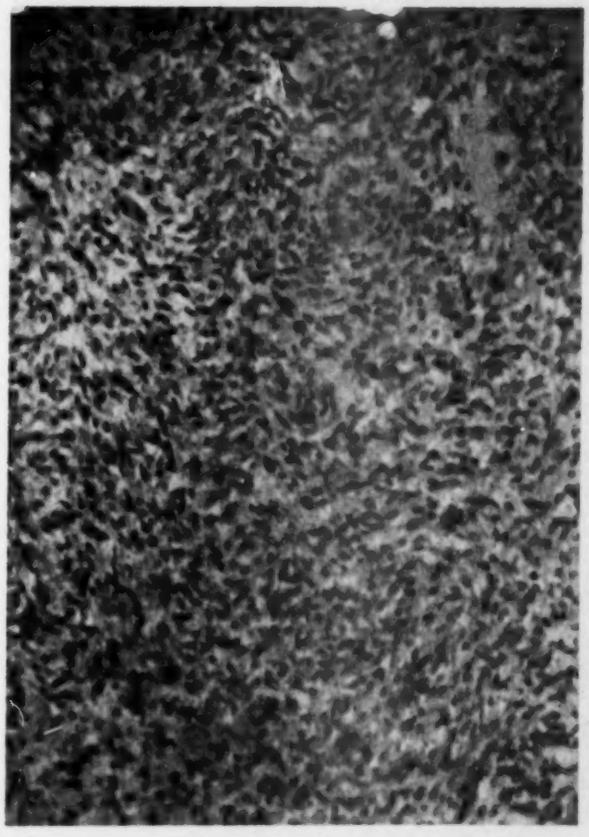


FIG. 3. Note strands and whorls of spindle cells in the fibrous portion of the tumor. Hematoxylin and eosin, × 250.

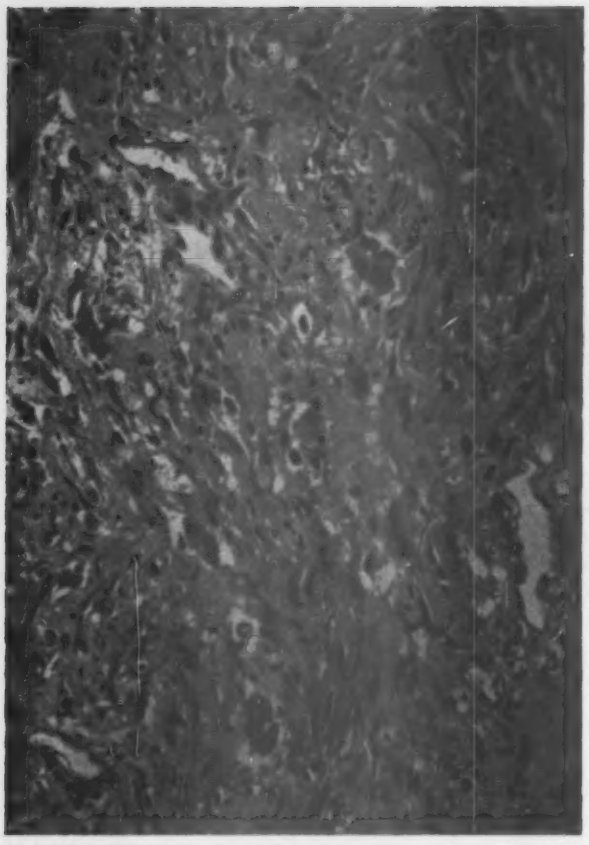


FIG. 4. Note less dense areas of the tumor showing clefts lined by plump epithelial cells. Hematoxylin and eosin, × 250.

pulmonary vessels without invasion of the lung parenchyma or hilar lymph nodes. According to the criteria of Dawe, Wood and Mitchell[3] this tumor may be classified as a mixed mesothelioma of the pericardium since it consists of significant portions of both spindle cells and epithelial elements.

COMMENT

It appears from recent studies that neoplastic invasion of the heart is more frequent than was formerly believed and should be given consideration in the differential diagnosis of heart disease. Establishing the diagnosis of primary tumor of the pericardium is most difficult for there is no specific symptomatology associated with pericardial tumors. There are, however, several groups of findings which may suggest such a diagnosis. Among these are persistent edema; hepatomegaly and increased venous pressure, which accompany refractory right-sided heart failure; narrowed pulse pressure and paradoxical pulse characteristic of cardiac compression or tamponade; unexplained chest pain; bizarre cardiac enlargement; signs of superior vena caval obstruction and mediastinal tumor. A less frequent finding, but of greater significance, is recurrent sanguinous pericardial effusion in the absence of tuberculosis.[12]

Chest roentgenograms, cardiac fluoroscopy and serial electrocardiograms are excellent adjuncts in the diagnosis. In negating similar confusing cardiac diagnoses routine hematologic studies, blood chemistries and serum enzyme studies, serology, antistreptolysin O and cold agglutinins may be helpful. Pericardial paracentesis, with bacteriologic and cytologic examination of the aspirated fluid, is of great value when effusion is suspected or demonstrated by fluoroscopy. At this time, air may be injected into the pericardial cavity to further delineate the thickness and contour of the pericardium. Direct pericardial biopsy is certainly useful but not as practical as other means. More specialized studies, not universally available but which will contribute much in obscure cases, are angiocardiography, kymography and cinematofluorography of the heart.

In the present case there was evidence of refractory right-sided heart failure with bizarre cardiomegaly, pericardial compression and symptomatology suggestive of coronary occlusion. Fluoroscopic and electrocardiographic findings were compatible with the diagnosis of pericardial tumor as outlined. Unfortunately, the sudden death of the patient precluded the contemplated pericardial paracentesis and the possibility of an antemortem diagnosis of a primary tumor of the pericardium.

SUMMARY

A case is presented in which the predominant features were right-sided heart failure, bizarre cardiac enlargement and symptoms of coronary occlusion. Postmortem examination revealed a primary mixed mesothelioma of the pericardium.

REFERENCES

1. BRANDES, W. W., GRAY, J. A. C. and MACLEOD, N. W. Leiomyoma of the pericardium. *Am. Heart J.*, 23: 426, 1942.
2. COHEN, G. U., PEERY, T. M. and EVANS, J. M. Neoplastic invasion of the heart and pericardium. *Ann. Int. Med.*, 42: 1238, 1955.
3. DAWE, C. J., WOOD, D. A. and MITCHELL, S. Diffuse fibrous mesothelioma of the pericardium. *Cancer*, 6: 794, 1953.
4. FRIEDBERG, C. K. Diseases of the Heart. 2nd Ed., p. 1071. Philadelphia, 1956. W. B. Saunders Co.
5. GLASSY, F. J. and MASSEY, F. C. Primary hemangio-endothelial sarcoma of the heart. *Am. J. Med.*, 8: 544, 1950.

6. Hochberg, L. A. and Robinson, A. I. Primary tumors of the pericardium involving the myocardium. *Circulation*, 1: 805, 1950.
7. Parker, R. L., Baggenstoss, A. H. and Dry, T. J. Primary sarcoma of the pericardium. *Arch. Int. Med.*, 65: 51, 1940.
8. Reals, W. J., Russum, B. C. and Walsh, E. M. Primary mesothelioma of the pericardium. *Arch. Path.*, 44: 380, 1947.
9. Sarrell, W. G. Primary pericardial mesothelioma. *Am. Heart J.*, 49: 310, 1955.
10. Scott, R. W. and Garvin, C. F. Tumors of the heart and pericardium. *Am. Heart J.*, 17: 431, 1939.
11. Steuer, L. J. and Higley, C. S. Primary sarcoma of the pericardium. *J. A. M. A.*, 105: 1110, 1935.
12. Thomas, J. and Phythyon, J. M. Primary mesothelioma of the pericardium. *Circulation*, 15: 385, 1957.
13. Yater, W. M. Tumors of the heart and pericardium. *Arch. Int. Med.*, 48: 627, 1931.

Progress Notes in Cardiology

Edited by EMANUEL GOLDBERGER, M.D., F.A.C.C.
New York, New York

Cardiac Failure in Infants and Children

THE etiology and therapy of congestive heart failure in infants and children are different from those in adults. Several recent articles have dealt with this problem.

The first paper, by Drs. Anna J. Hauk and Alexander S. Nadas of the Children's Medical Center, Boston (Cardiac Failure in Infants and Children, Pediatric Clinics of North America, November 1958), describes the clinical features encountered in seventy-seven infants and children with cardiac failure and outlines the steps to be taken in treating cardiac decompensation in young patients.

Congenital heart disease was the cause of failure in sixty-two of seventy-seven patients. The etiology in the remainder of cases included myocardial disease, renal disease with hypertension and anemia, severe anemia secondary to neoplasm and arrhythmia. The combination of tachycardia, tachypnea and hepatomegaly occurred in most patients. Pulmonary rales were found in approximately a third of the group. Peripheral edema was less common and was seen in only fourteen children. Distended neck veins were observed in seventeen patients. In very young patients, however, this sign was difficult to demonstrate because of the abundance of adipose tissue and shortness of the neck.

In the hands of the authors, digoxin has been a useful cardiac glycoside in the pediatric age group. Young children require more of the drug per pound than older ones. The recommended schedule for the initial digitalization of infants from the newborn period to two years of age is 0.03 to 0.04 mg. digoxin per pound administered in three or four divided doses over twenty-four hours. For children beyond two years of age, the dose is 0.02 to 0.03 mg. per pound administered in a similar way. However, if a good clinical response does not occur, then one-fourth of the total digitalizing dose should be given every six to eight hours until improvement or signs of toxicity appear. The procedure of digitalization should be monitored closely by the electrocardiogram, since the first sign of toxicity often is seen there, rather than clinically. Once digitalization has been completed, a maintenance dosage of one-fourth to one-third of the digitalizing dose, given in two divided doses over twenty-four hours, may be started. If clinical improvement does not persist, the daily dose should be increased until the patient has improved or mild toxicity appears, often in the form of a prolonged P-R interval. The authors found that maximal benefit from this glycoside was achieved only by following the patient's course and adjusting the dosage accordingly rather than following the described schedule rigidly.

If failure is severe, diuretics may also be used. Both the organomercurials and chlorothiazide, the latter supplemented by potassium chloride, are effective. In addition, sodium restriction may be necessary if failure is difficult to control. Low sodium milk seems to be readily accepted by most young patients. If the child is in acute distress, the usual emergency measures used in adults should be employed. These include the administration of oxygen and morphine, rotation of tourniquets on the extremities, maintaining the child in a sitting position, and possibly venesection.

Once the initial treatment has been carried out, attention should be directed to establishing the cause of failure in each child. Since surgical correction is now available for many types of congenital heart disease, cardiac catheterization should be considered, so that an exact diagnosis can be made. Other conditions amenable to therapy should also be sought. These include arrhythmias, anemia, pericardial effusion, and hypertension. If active rheumatic

fever is the cause of failure, then the question of therapy with adrenal steroids or salicylates should be considered.

* * *

Infants and children have many complicated problems involving fluid therapy. These, as well as the etiology and therapy of heart failure, have been excellently summarized in a recent volume: Fluid and Electrolyte Problems. Pediatric Clinics of North America, Vol. 6, No. 1. Philadelphia, 1959. W. B. Saunders Co.

M. A. Engle (New York Hospital, New York) has a paper on Fluid Therapy in Congestive Circulatory Failure (p. 241) which is of particular interest to cardiologists. Not only are the problems of digitalis and diuretic dosage discussed, but the following table is also presented:

Causes of Cardiac Failure

Infancy (0–12 Months)		*Childhood (1–14 Years)*	
Gradual, Predictable	Sudden, Unexpected	Gradual, Predictable	Sudden, Unexpected
Congenital malformations, especially: Complete transposition of great vessels Ventricular septal defect, large Coarctation of aorta with patent ductus and often with ventricular septal defect Total anomalous pulmonary venous return to right atrium or tributary Atrioventricular canal Patent ductus arteriosus, large Aortic or mitral atresia Single ventricle Anemia, severe	Paroxysmal supraventricular tachycardia Endocardial fibroelastosis Myocarditis Pericarditis with effusion Severe respiratory infections, as bronchiolitis Abrupt circulatory overloading from excessive parenteral fluids or transfusion Infants born to diabetic mothers Coronary artery disturbances: Anomalous origin of coronary artery from pulmonary artery Coronary sclerosis Glycogen storage disease of myocardium Cardiac tumors	Rheumatic heart disease Hypertensive cardiovascular disease with chronic severe renal disease Anemia, severe, chronic, and especially with associated hemochromatosis Cor pulmonale with cystic fibrosis of pancreas Hyperthryoidism Congenital cardiac anomalies plus severe infection Others, such as lupus erythematosus, neuromuscular dystrophies, etc.	Acute glomerulonephritis Acute rheumatic fever Myocarditis Pericarditis with effusion

Book Reviews

Diagnosis of Congenital Heart Disease, 2nd ed., by Sven R. Kjellberg, Edgar Mannheimer, Ulf Rudhe and Bengt Jonsson. The Year Book Publishers, Chicago, 1959, pp. 833, $28.00.

The second edition of this well received volume is somewhat more complete than its predecessor, published in 1955.

The material covered has been expanded to include a detailed analysis of 742 cases of congenital heart disease as compared to the 396 cases analyzed in the first edition. New sections have been added which include: the effects of exercise in various congenital heart lesions; pulmonary atresia with intact ventricular septum; stenosis or atresia of the branches of the pulmonary artery; corrected transposition of the great vessels; and communication between the left atrium and the coronary sinus.

The volume presents the clinical, electrocardiographic, catheterization, phonocardiographic, electrokymographic, roentgenologic and angiocardiographic data obtained in children with congenital heart disease studied in one of the outstanding institutions in this field, the Karolinska Sjukhuset. The detailed information obtained is lucidly presented and this book should serve as a standard reference work in the future.

Since two of the authors are roentgenologists, the book is noticeably strong, and probably without equal, in its presentation of the roentgenologic and angiocardiographic manifestations of the various entities described. Liberal use of illustrations and outstanding chapters on embryology and "roentgenologic anatomy" give the book unique value. Analysis of electrokymograms should provide information not readily available to American readers, as this technic has not been widely employed in the United States in the investigation of congenital heart disease.

On the other hand, the use of dye dilution curves and the employment of radioactive substances, which have been gaining increasing popularity in analyzing congenital cardiac malformations, have not been employed in the cases presented. Vectorcardiographic analysis has also been omitted. Although the scope of the volume is large, there are no data presented concerning congenital anomalies of the coronary arteries, endocardial fibroelastosis or the various types of dextrocardia. Data on left heart catheterization in aortic stenosis are scanty, since this procedure was performed in only three of twenty-three cases.

Since analysis of the surgical treatment of these conditions is beyond the scope of this volume, those with a casual interest in the field, desiring a single volume covering all aspects of congenital heart disease, might wish to look elsewhere. For those interested in detailed diagnostic studies, particularly in the spheres of standard roentgenology and angiocardiography, this should prove to be an exceedingly valuable volume.

LESLIE A. KUHN, M.D.

RECEIVED FOR REVIEW

All books received will be acknowledged in this column. Insofar as possible, as space permits, books of special interest will receive more extensive reviews.

Involution of the Ductus Arteriosus, by A. Scicca and M. Condorelli. S. Karger AG, Basel, 1960, pp. 52, sFr.7.

Elektroanatomie des menschlichen Herzens. I. Teil, by Franz A. L. Kienle. Verlag Wolfgang Weidlich, Frankfurt, 1959, pp. 13 plus 110 illustrations, DM 24.

Acute Pericarditis, by David H. Spodick. Grune & Stratton, New York, 1959, pp. 182, $6.50.

Electrical Impedance Plethysmography: The Electrical Resistive Measure of the Blood Pulse Volume, Peripheral and Control Blood Flow, by Jan Nyboer. Charles C Thomas, Springfield, Ill., 1959, pp. 243, $7.50.

Isolated Pulmonary Stenosis. Signs and Symptoms, Course and Results of Operation in 75 Cases Diagnosed at Cardiac Catheterization, by Jørgen Fabricus. Ejnar Munksgaard, Copenhagen, Denmark, 1959, pp. 203, dan. Kr. 30.00.

Arterial Embolism in the Limbs. The Clinical Problem and its Anatomical Basis, by A. L. Jacobs. E. & S. Livingstone Ltd., Edinburgh, 1959 (Williams & Wilkins, exclusive American agents), pp. 200, $8.00.

Antithrombotic Therapy, by Paul W. Boyles. Grune & Stratton, New York, 1959, pp. 131, $5.00.

Autogenous Vein Grafts and Related Aspects of Peripheral Arterial Disease, by W. Andrew Dale. Charles C Thomas, Springfield, Ill., 1959, pp. 123, $6.00.

Diseases of the Chest Including the Heart, edited by J. Arthur Myers. Charles C Thomas, Springfield, Ill., 1959, pp. 1015, $34.50.

College News

1960 Workshop Programs

After careful discussions and considerations by Dr. Joseph B. Wolffe, Chairman in Charge of Clinical Workshops, Dr. I. Frank Tullis, Chairman Professional Education Committee and Dr. Eliot Corday, Chairman in charge of Postgraduate courses, it has been decided to limit this year's program to a selected schedule of six important workshops which are believed to be particularly attractive to members of the College.

Those who attended the last workshop held in Mexico under Dr. Chavez' preceptorship remember the sessions with particular delight. Dr. Chavez will lead another workshop and Dr. Wolffe will most probably accompany the College group making the trip to Mexico.

The Workshop Program is not only edifying and valuable but represents the realization of one of the College's most fundamental raisons d'etre.

Members of the College are uged to take advantage of this opportunity offered by your Postgraduate Education Committee by communicating with Dr. Philip Reichert, Executive Secretary, 350 Fifth Ave., New York 1, New York, relative to arrangements for participation. Due to the limited number of students for each workshop, early registration is advised.

Clinical Workshop Program 1960

Date (1960)	Preceptor	Subject	Place	Maximum No. of Students
February 9, 10, 11	Dr. Ignacio Chavez	Broad aspects of meeting cardiologic problems; diagnosis and treatment	National Heart Institute, Mexico, D. F., Mexico	10
May 16–22	Dr. Benjamin Gasul	What we must know about congenital heart disease; diagnosis and management	Cook County Children's Hospital 700 South Wood Street Chicago, Ill.	8
March 31 (Tentative)	Dr. Emanuel Goldberger	How to determine if a cardiac patient (congenital or acquired) will benefit from cardiac surgery	Montefiore Hospital 210th St. and Bainbridge Ave. New York, N. Y.	8
April 10–16	Dr. Robert P. Glover	Intimate contact with problems of diagnosis and treatment of patients suitable for cardiac surgery (possibility of scrubbing with Dr. Glover)	The Glover Clinic 269 S. 19th St. Philadelphia 3, Pa.	3
June 6–11	Dr. Oscar Magidson	Indications and contraindications to open heart surgery; practical considerations	St. Vincent's Hospital 2131 W. 3rd St. Los Angeles 57, Calif.	8
June 9, 10	Dr. Ashton Graybiel	Stress and the cardiovascular system in space medicine	U. S. Naval Aviation Medical Center Pensacola, Fla.	5

Announcements

National Resuscitation Society News

Following the Twenty-Sixth Annual Meeting of the National Resuscitation Society, Inc., held in New York City Wednesday evening, October 14, 1959, the following appointments were announced:

For President:
MAJOR GENERAL GEORGE E. ARMSTRONG, Chief Administrative Officer, New York University Bellevue Medical Center, and former Surgeon General of the United States Army.

For Vice-President:
CLAUDE S. BECK, M.D., Professor of Cardio-Vascular Surgery, Western Reserve Medical School, Cleveland.

For Secretary:
CAPTAIN ROBERT V. SCHULZ, M.C., U.S.N., Head of Audio-Visual Department, United States Navy, Washington, D.C.

To the Advisory Board:
JAMES R. CAMERON, D.D.S., SC.D., LL.D., Professor of Oral Surgery, School of Dentistry, Temple University, Philadelphia.

To the Board of Directors:
ROBERT M. HOSLER, M.D., Director, Cleveland Cardiac Resuscitation Course, Cleveland.

It was also announced that more than fifty Heart Associations are now actively interested in the intensive course in Respiro-Cardiac Resuscitation sponsored by the National Resuscitation Society in conjunction with the American College of Cardiology. The course is held every two months in New York City and occasionally out of town. Heart Societies, it was reported, have, over the last eighteen months, contributed more than one hundred scholarships (seventy-five dollars each) to physicians and operating room supervisors in their respective areas. Information concerning these courses may be had from the Secretary, N.R.S., Inc., 2 East 63 Street, New York 21, New York.

It is anticipated that this news release will shortly result in a strong Lay Board, a rapidly increasing membership and improved organizational facilities.

The Sixth Biennial Cardiovascular Seminar

The Sixth Biennial Cardiovascular Seminar will be held at the Balmoral Hotel, Miami Beach, Florida, April 27–30, 1960. Co-sponsored by the Florida Heart Association, the Florida State Board of Health and the Heart Association of Greater Miami, Inc., the Seminar's Faculty is composed of well known physicians throughout the United States. This Seminar will feature, in addition to lectures, small discussion groups with members of the Faculty. For further details, write to the Heart Association of Greater Miami, 2 S.E. 13th Street, Miami 32, Florida.

Sixth Inter-American Congress of Cardiology

The Inter-American and Brazilian Societies of Cardiology (Dr. Magathaes Gomes, President) announce the Sixth Inter-American Congress of Cardiology to be held in Rio de Janeiro, Brazil, August 14–20, 1960. All communications should be addressed to Dr. HUGO ALQUERES, P. O. Box 1594, Secretary of the Congress, P. O. Box 1594, Rio de Janeiro, Brazil.

The Chicago Round Table of the American College of Cardiology

A group of Fellows of the College in the State of Illinois, following the initiative of Dr. Maximilian Kern, organized in 1958 the "Round Table" of the College. This is a group of members in good standing who gather once a month for dinner and discussion of a special topic of Cardiology.

Among the lecturers during the last eighteen months were Drs. Gasul, Graettinger, Kezdi, Luisada, Lundy, Priest, Smith and Wehrmacher. Lecturers not members of the College were James Campbell, John Lewis and others. The Secretary of the College, who was visiting Chicago, gave a fine impromptu talk, and was elected as Honorary Member of the Round Table.

About thirty members pay nominal dues to this group and between twelve and twenty of them are present on each occasion.

This group has served to cement the personal relationships between local members of the College, and has proved to be a useful and pleasant channel for exchange of cardiological information.

An emotionally balanced patient. Thanks to your treatment and the help of Deprol, her depression is relieved and her anxiety and tension calmed. She eats well, sleeps well, and can return to her normal activities.

Lifts depression...as it calms anxiety!

Deprol helps balance the mood by lifting depression as it calms related anxiety

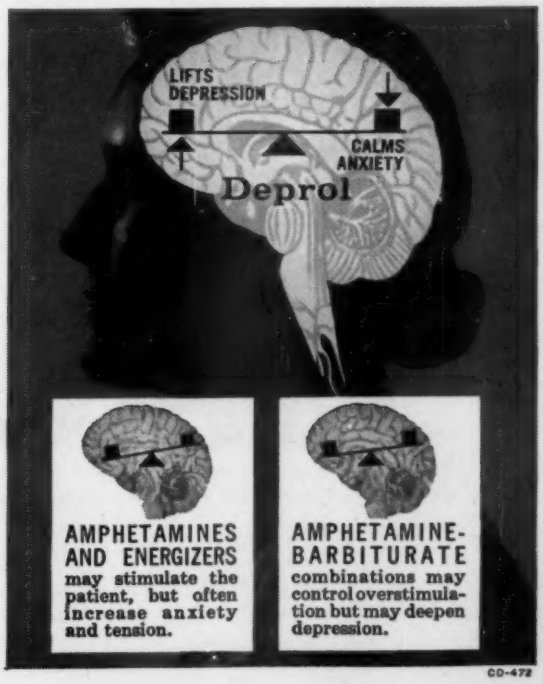
No "seesaw" effect of amphetamine-barbiturates and energizers

While amphetamines and energizers may stimulate the patient — *they often aggravate anxiety and tension.* And although amphetamine-barbiturate combinations may counteract excessive stimulation — *they often deepen depression.*

In contrast to such "seesaw" effects, Deprol lifts depression as it calms anxiety—both at the same time.

Safer choice of medication than untested drugs

Deprol does not produce hypotension, liver damage, psychotic reactions or changes in sexual function.



CD-472

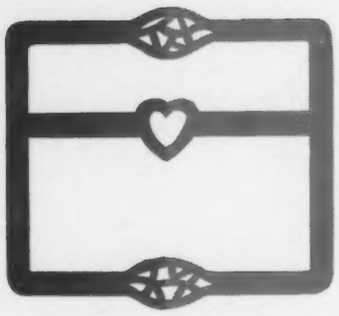
Deprol®

WALLACE LABORATORIES
New Brunswick, N. J.

Dosage: Usual starting dose is 1 tablet q.i.d. When necessary, this may be gradually increased up to 3 tablets q.i.d.

Composition: 1 mg. 2-diethylaminoethyl benzilate hydrochloride (benactyzine HCl) and 400 mg. meprobamate.

Supplied: Bottles of 50 light-pink, scored tablets. Write for literature and samples.



FOR GREATER LATITUDE IN SOLVING THE PROBLEM **HYPERTENSION** WITHOUT SIGNIFICANT POTASSIUM DEPLETION

NEW RAUTRAX

RAUTRAX, a combination of Raudixin with Ademol (flumethiazide)—**the new, safe nonmercurial diuretic**—controls all degrees of hypertension. Elimination of excess extracellular sodium and water is rapid and safe.[1-5] Potassium loss is less than with other nonmercurial diuretics;[1-3] and, in addition, Rautrax increases protection against potassium and chloride depletion during long-term management by including supplemental potassium chloride.

The dependable diuretic action of Ademol rapidly controls the clinical and subclinical edema often associated with cardiovascular disease. And after Rautrax has normalized the fluid balance, the normal serum electrolyte pattern is not altered appreciably by continued administration.[4] Ademol also potentiates the antihypertensive action of Raudixin.[1] In this way a lower dose of each component controls hypertension effectively and safely . . . with fewer side effects.

REFERENCES: 1. Montero, A. C.; Rochelle, J B., III, and Ford, R.V.: New England J. Med 260:872 (April 23) 1959. 2. Fuchs, M.; Bodi, T., and Moyer, J. H.: Am. J. Cardiol. 3:676 (May) 1959. 3. Fuchs, M., and others: Monographs on Therapy 4:43 (April) 1959 4. Montero, A. C.; Rochelle, J. B., III, and Ford, R V.: Am. Heart J 57:484 (April) 1959. 5. Rochelle, J B., III; Montero, A. C., and Ford, R. V.: Antibiotic Med. & Clin. Ther. 6:267 (May) 1959. LITERATURE AVAILABLE ON REQUEST

SQUIBB

Squibb Quality—
the Priceless Ingredient

RAUDIXIN (Squibb standardized whole root Rauwolfia Serpentina) / **ADEMOL** (Squibb Flumethiazide) / **POTASSIUM CHLORIDE**

'RAUDIXIN', ®, 'RAUTRAX' AND 'ADEMOL' ARE SQUIBB TRADEMARKS

In Coronary Insufficiency...

Your high-strung angina patient often expends a "100-yd. dash" worth of cardiac reserve through needless excitement.

Curbs emotion as it boosts coronary blood supply

CONTROL OF EMOTIONAL EXERTION with Miltrate leaves him more freedom for physical activity.

IMPROVED CORONARY BLOOD SUPPLY with Miltrate increases his exercise tolerance.

Miltrate*

Miltown® (*meprobamate*) + PETN

Each tablet contains: 200 mg. Miltown and 10 mg. pentaerythritol tetranitrate.
Supplied: Bottles of 50 tablets.
Usual dosage: 1 or 2 tablets q.i.d. *before meals* and at bedtime. Dosage should be individualized.

WALLACE LABORATORIES · *New Brunswick, N. J.*

CML-9169-59 *TRADE-MARK

"First in the hearts"
of cardiac patients

A.C.M.I.

CARDIAC CATHETERS

A.C.M.I. was the first to introduce nylon woven catheters in the United States – originally for ureteral use – later for cardiac catheterization.

A.C.M.I.'s nylon woven cardiac catheters are preferred for smoothness combined with flexibility. Lengths: 30 cm. to 150 cm. Thin-walled, radiopaque.

A.C.M.I.'s polyethylene cardiac catheters provide a smoother and larger lumen for collection of blood samples and the rapid injection of contrast media. Other types too are under development.

A triumph of technical skill – all A.C.M.I. cardiac catheters have earned the confidence of the medical profession through their consistently superior quality.

Nylon woven cardiac catheters

A·C·M·I
TRADE MARK

FREDERICK J. WALLACE, *President*

American Cystoscope Makers, Inc.

8 PELHAM PARKWAY, PELHAM MANOR, N. Y.

A museum guard, a lecturer and a salesman may not have anything in common except angina pectoris. As angina patients, they share a common need for Peritrate 20 mg. q.i.d.—"basic therapy" providing long-acting coronary vasodilatation for fewer, less severe attacks, increased exercise tolerance, reduced nitroglycerin dependence and improved ECG findings.

As individuals, however, their needs vary, so that therapy in one should also include relief of tension, while another may require convenience of administration. Broad coverage protection for each patient is afforded by a Peritrate formulation in terms of

adaptable
prophylaxis in
angina
pectoris with **Peritrate® 20 mg.**

brand of pentaerythritol tetranitrate

basic therapy in coronary artery disease:

Peritrate 20 mg. with **Phenobarbital** for the **apprehensive patient** (q.i.d.).

Peritrate **Sustained Action** for convenient **24-hour protection** (one tablet in the morning, one 12 hours later).

WARNER
CHILCOTT

MORRIS PLAINS, N. J.

PE QP 01

'CARDILATE'

'CARDILATE'
SUBLINGUAL TABLETS

ANGINA PECTORIS

"Nitroglycerin and erythrol tetranitrate when administered sublingually are among the most effective of all prophylactic agents available for the treatment of patients with angina pectoris. The comparatively prolonged duration of action of erythrol tetranitrate makes it especially valuable for clinical use."

Riseman, J. E. F., *et al.*: Circulation *17*:22, 1958

Sublingual administration obviates inactivation of nitrites in gastrointestinal tract.

Most closely approximates nitroglycerin in frequency and degree of effectiveness.

'Cardilate' brand Erythrol Tetranitrate Sublingual Tablets 15 mg., scored.

BURROUGHS WELLCOME & CO. (U.S.A.) INC.
Tuckahoe, New York

Singoserp:

It spares them from the usual rauwolfia side effects

FOR EXAMPLE: "A clinical study made of syrosingopine [Singoserp] therapy in 77 ambulant patients with essential hypertension demonstrated this agent to be effective in reducing hypertension, although the daily dosage required is higher than that of reserpine. Severe side-effects are infrequent, and this attribute of syrosingopine is its chief advantage over other Rauwolfia preparations. The drug appears useful in the management of patients with essential hypertension."*

*Herrmann, G. R., Vogelpohl, E. B., Hejtmancik, M. R., and Wright, J. C.: J.A.M.A. 169:1609 (April 4) 1959.

Singoserp®

(syrosingopine CIBA)

First drug to try in new hypertensive patients

First drug to add in hypertensive patients already on medication

SUPPLIED: Singoserp *Tablets*, 1 mg. (white, scored); bottles of 100. Samples available on request. Write to CIBA, Box 277, Summit, N. J.

CIBA
SUMMIT, N. J.

3/2697M8

A well-balanced moderate low-fat breakfast for teen-age girls, 16-19 years

When a moderate reduction of dietary fat is indicated for girls in their late teens, the basic cereal and milk breakfast merits consideration. *This breakfast is moderately low in fat because its fat content of 10.9 gm. provides 20 per cent of the total calories.* As shown in the table below, it contributes *well-balanced nourishment.* It provides "Girls, 16 to 19 Years" with approximately one-fourth of the recommended dietary allowances[1] of complete protein, important B vitamins, essential minerals; and provides quick and lasting energy.

recommended dietary allowances and the nutritional contribution of a moderate low-fat breakfast*

Menu: Orange Juice—4 oz.;
Cereal, dry weight—1 oz.;
Whole Milk—4 oz.; Sugar—1 teaspoon;
Toast (white, enriched)—2 slices;
Butter—5 gm. (about 1 teaspoon);
Nonfat Milk—8 oz.

Nutrients	Calories	Protein	Calcium	Iron	Vitamin A	Thiamine	Riboflavin	Niacin equiv.	Ascorbic Acid
Totals supplied by Basic Breakfast**	503	20.9 gm.	0.532 gm.	2.7 mg.	588 I.U.	0.46 mg.	0.80 mg.	7.36 mg.	65.5 mg.
Recommended Dietary[1] Allowances—Girls, 16 to 19 Years (54 kg.—120 lb.)	2400	75 gm.	1.3 gm.	15 mg.	5000 I.U.	1.2 mg.	1.9 mg.	16 mg.	80 mg.
Percentage Contributed by Basic Breakfast	20.9%	27.9%	40.9%	18.0%	11.8%	38.3%	42.1%	46.0%	81.9%

**Revised 1958, Food and Nutrition Board, National Research Council, Washington, D.C.*

***Cereal Institute, Inc.: Breakfast Source Book. Chicago: Cereal Institute, Inc., 1959.*
Watt, B. K., and Merrill, A. L.: Composition of Foods—Raw, Processed, Prepared. U.S.D.A. Agriculture Handbook No. 8, 1950.

[1]The allowance levels are intended to cover individual variations among most normal persons as they live in the United States under usual environmental stresses. Calorie allowances apply to individuals usually engaged in moderate physical activity. For office workers or others in sedentary occupations they are excessive. Adjustments must be made for variations in body size, age, physical activity, and environmental temperature.

CEREAL INSTITUTE, INC.
135 South La Salle Street, Chicago 3

A research and educational endeavor devoted to the betterment of national nutrition

in acute cardiac arrhythmias

VISTARIL®

hydroxyzine pamoate

can restore normal sinus rhythm...sometimes within minutes

The gentle tranquilizing effect of VISTARIL dispels fear and anxiety and rapidly reassures cardiac arrhythmia patients.

In addition, VISTARIL appears to act directly on the myocardium. Normal sinus rhythm is frequently restored and maintained.

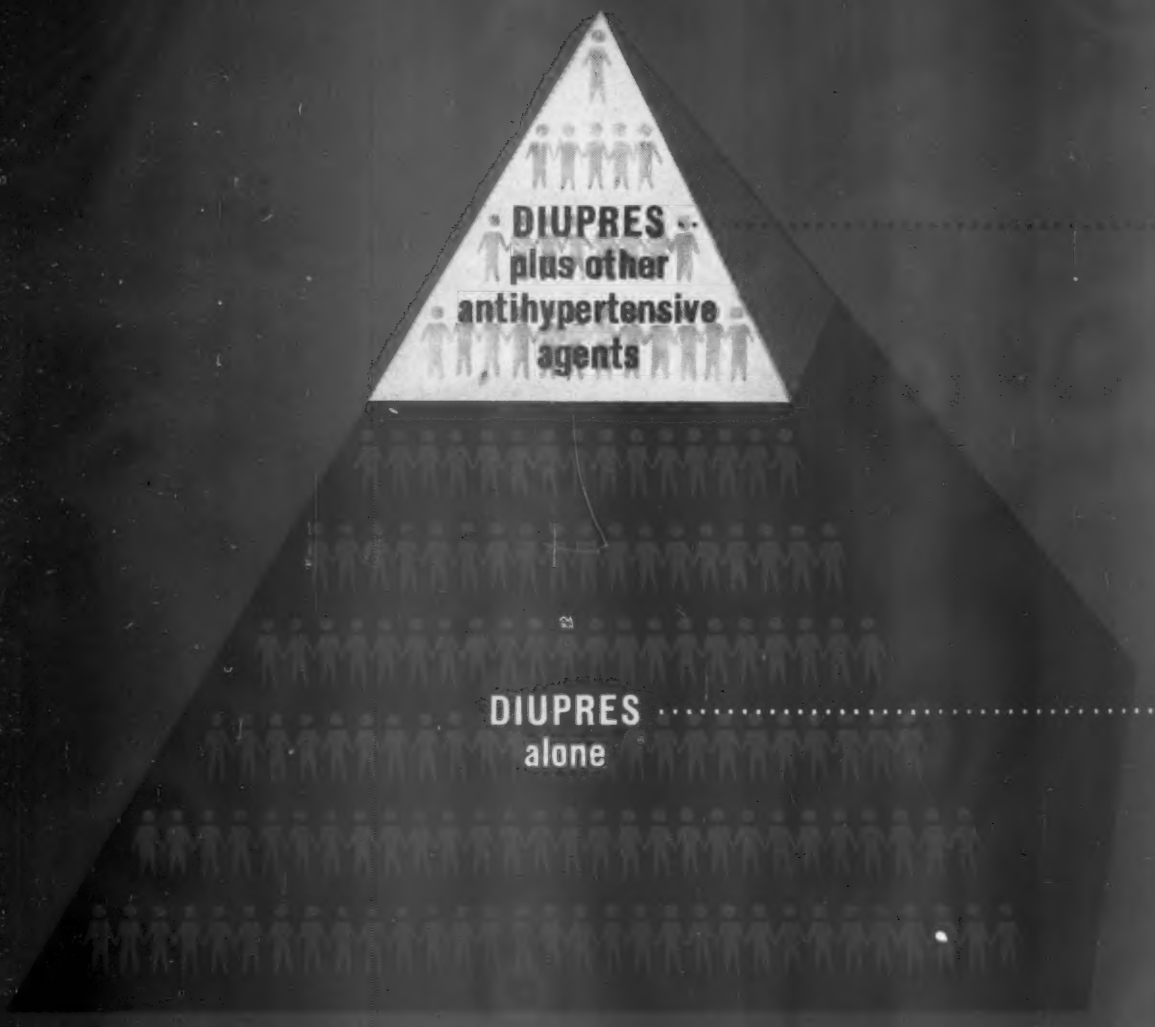
Therapeutically, VISTARIL is particularly effective in arrhythmias of sudden onset.

Prophylactically, VISTARIL may decrease or entirely prevent the number of attacks of paroxysmal auricular tachycardia or fibrillation.

Further information is available from the Medical Department on request.

Pfizer *Science for the world's well-being™*

PFIZER LABORATORIES, Div., Chas. Pfizer & Co., Inc., Brooklyn 6, New York



with DIUPRES, fewer patients require addition of other anti-hypertensive agents

DIUPRES is adequate by itself for many hypertensives

DIUPRES PROVIDES "BROAD-BASE" ANTIHYPERTENSIVE THERAPY

... is effective by itself in a majority of patients with mild or moderate hypertension, and even in many with severe hypertension

greatly improved and simplified management of hypertension

DIUPRES*

DIURIL® WITH RESERPINE

the first "wide-range" antihypertensive—effective in mild, moderate, and severe hypertension

- more hypertensives can be better controlled with DIUPRES alone than with any other agent... with greater simplicity and convenience, and with decreased side effects
- can be used as total therapy or primary therapy, adding other drugs if necessary
- in patients now treated with other drugs, can be used as replacement or adjunctive therapy
- should other drugs need to be added, they can be given in much lower than usual dosage so that their side effects are often strikingly reduced
- organic changes of hypertension may be arrested and reversed... even anginal pain may be eliminated
- patient takes one tablet rather than two... dosage schedule is easy to follow
- economical

DIUPRES-500 500 mg. DIURIL (chlorothiazide), 0.125 mg. reserpine.
One tablet one to three times a day.

DIUPRES-250 250 mg. DIURIL (chlorothiazide), 0.125 mg. reserpine.
One tablet one to four times a day.

MERCK SHARP & DOHME, DIVISION OF MERCK & CO., INC., PHILADELPHIA 1, PA.

* DIUPRES AND DIURIL (CHLOROTHIAZIDE) ARE TRADEMARKS OF MERCK & CO., INC.

Doctor, do you feel that your colleagues are missing important new developments in cardiology by not reading The American Journal of Cardiology?

Let us send them a complimentary copy—of course there is no obligation to you or your colleagues. Just fill out the coupon and mail it to us

*Dr.*_____ *Dr.*_____

*Address*_____ *Address*_____

_____ _____

*Dr.*_____ *Your Name*_____

*Address*_____ *Address*_____

_____ _____

The American Journal of Cardiology

11 EAST 36th STREET NEW YORK 16, NEW YORK

The first specific aldosterone-blocking agent...

ALDACTONE™

BRAND OF SPIRONOLACTONE

Effectively extends the medical control of edema and ascites. It introduces a new therapeutic principle in treatment of...

CONGESTIVE HEART FAILURE

HEPATIC CIRRHOSIS

THE NEPHROTIC SYNDROME

IDIOPATHIC EDEMA

ALDACTONE introduces a new class of therapeutic agent, the aldosterone antagonist, having a new kind of therapeutic activity. It specifically blocks an altered physiologic mechanism which has caused excessive sodium and water retention, thus achieves diuresis. This activity provides a fundamentally new approach to the control of edema and ascites, including edema totally or partially refractory or unresponsive to all other diuretic agents.

G. D. SEARLE & CO.
CHICAGO 80, ILLINOIS
Research in the Service of Medicine

The advantages of

ALDACTONE™ *lie in:*

(a) a means for relieving resistant or advanced edema.

(b) highly useful synergistic activity in a program of treatment including conventional diuretic agents.

New...Pharmacologic Action

These advantages derive from a different *mode* of action and a different *site* of action than those of diuretic agents presently in use. Studies made during the past decade have demonstrated that the potent salt-retaining hormone, aldosterone, plays a fundamental role in regulating the reabsorption of sodium in the renal tubules. The production in the body of aldosterone increases strikingly in most edematous patients and plays a crucial role in producing and maintaining the edematous state in such disorders as congestive heart failure, hepatic cirrhosis, the nephrotic syndrome and idiopathic edema.

The new aldosterone-blocking agent, Aldactone, is a complex spirolactosteroid, closely resembling aldosterone in configuration. It arrests the activity of aldosterone and other mineralocorticoids which promote the retention of sodium and water, apparently by blocking their binding sites. Aldactone is thus able to establish a satisfactory diuresis in edematous patients who have heretofore been considered beyond the help of medical management with conventional diuretics.

G. D. SEARLE & CO. *Chicago 80, Illinois. Research in the Service of Medicine.*

New...Therapeutic Effect

Mercurial and thiazide compounds, presently the most widely used diuretic agents, apparently inactivate enzyme systems necessary to transport ions across the renal tubular epithelium. Both act mainly in the proximal convoluted tubules.

ALDACTONE™

acts by blocking hormone mediators (mineralocorticoids) governing the reabsorption of sodium and water and exerts its influence in the distal segment of the renal tubules. Aldactone is able to exert a beneficial therapeutic effect in two distinct ways:

1. Because it blocks an altered physiologic mechanism which has caused reabsorption of sodium, Aldactone may be used as the sole agent to produce a highly satisfactory diuresis.

2. Because of its different site and different mode of action, Aldactone has a true, highly valuable synergistic activity when used in a program of treatment that includes proximally acting diuretics.

New...Prevention of Potassium Loss

A distinct advantage of Aldactone in treating edema is its ability to conserve potassium during diuretic therapy. This property is particularly important in most edematous patients since hypokalemia may precipitate hepatic coma in those with cirrhosis, and digitalis intoxication in those taking digitalis.

It should be emphasized that Aldactone does not significantly affect an existing normal serum potassium level. When given as the sole agent, Aldactone averts the hypokalemia often induced by mercurial and thiazide diuretics, and when given in combination largely or wholly offsets the potassium loss which they induce.

For a preview of the change Aldactone is expected to make in the treatment of edema, please turn the page.→

What Physicians May Expect of

ALDACTONE™

It is fully expected that Aldactone will change present medical concepts of the therapeutic limitations in the management of edema. Many patients living in a greater or lesser state of edematous invalidism can now become edema-free. To others, gravely ill, Aldactone will be life-saving. Clinical trials demonstrate that, when used as the sole agent acting on the kidney in the relief of edema, Aldactone will produce a satisfactory diuresis in about half of those patients whose edema is intractable to conventional diuretic agents.

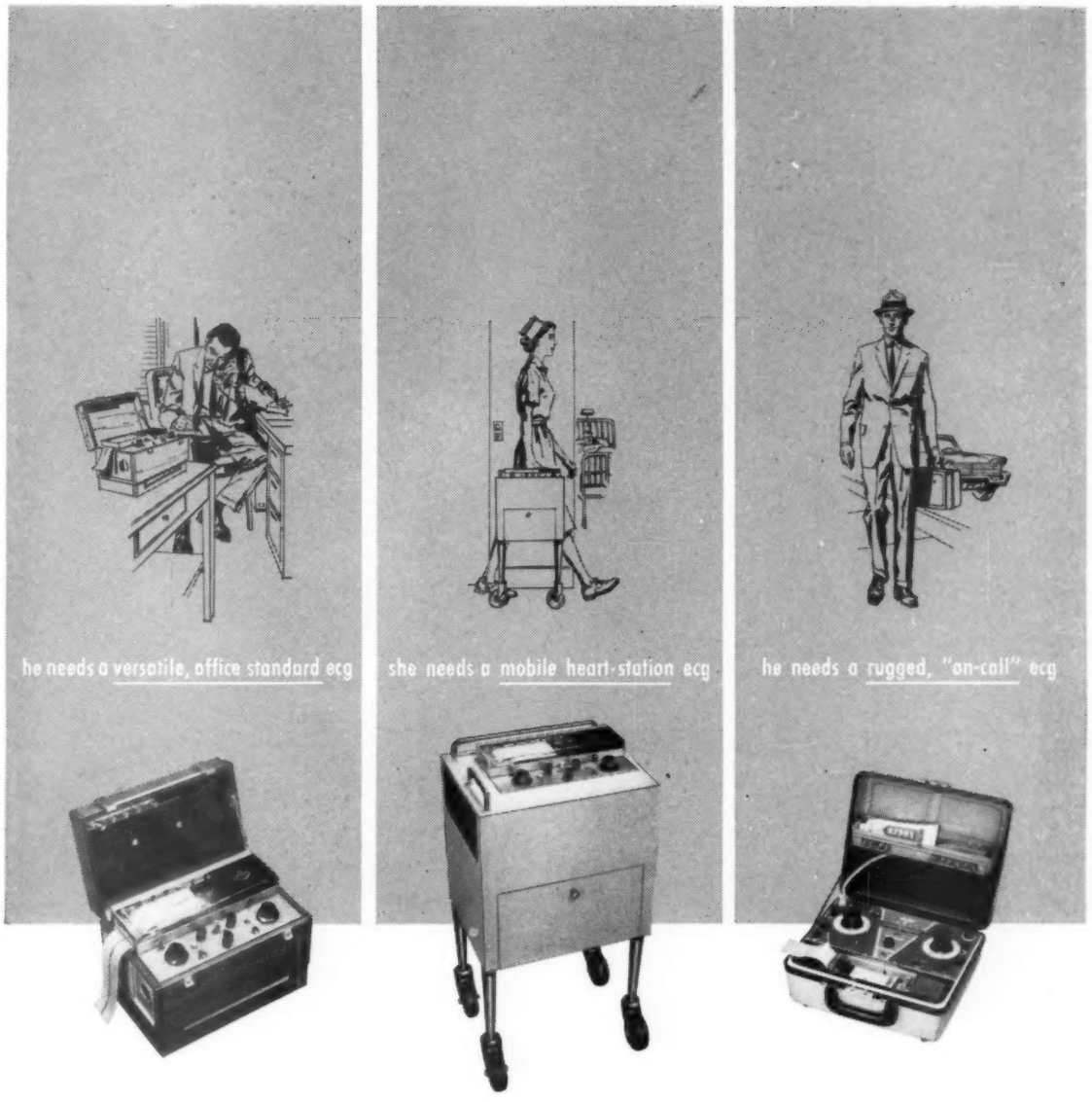
Furthermore, when Aldactone is used in conjunction with a mercurial or thiazide diuretic the level of satisfactory response may be expected to rise to approximately 85 per cent in those whose condition was refractory to all previously available therapeutic measures.

The response of some patients with extremely resistant edema may be further enhanced by administering a glucocorticoid such as prednisone. When Aldactone is used in such a comprehensive therapeutic regimen a satisfactory diuresis and relief of edema may be expected in more than 90 per cent of edematous patients *who would not otherwise respond.*

DOSAGE: For most adult patients the optimal dosage of Aldactone, brand of spironolactone, is 400 mg. daily in divided doses. Aldactone should be administered for at least four or five days before appraising the response, since the onset of its therapeutic effect is gradual when the drug is used alone. When used in combination with mercurial or thiazide diuretics Aldactone manifests greater activity on the first and second days. The dosage range is 300 to 1,200 mg. daily and dosage should be adjusted to the response of the patient. A dosage of 400 mg. daily, however, will meet the requirements of most patients, and even 800 mg. daily will seldom be required.

SUPPLIED: Aldactone is supplied as compression-coated yellow tablets of 100 mg.

G. D. SEARLE & CO., *Chicago 80, Illinois. Research in the Service of Medicine.*



only SANBORN makes all three

To the physician whose practice requires an "office standard" electrocardiograph of wide clinical usefulness, an instrument with such diagnostic advantages as two speeds, three recording sensitivities and provision for recording other phenomena will prove most logical. To the hospital nurse who must continually bring an electrocardiograph *to* the patient's bedside, no instrument is quite so useful as the completely self-contained, *mobile* one that can be effortlessly rolled in and out of elevators, up and down ramps and corridors. And to the doctor who must have an ECG that he can pick up and take on house calls, no instrument is useful unless it is *truly* portable—*and* completely dependable trip after trip.

To each of these people, Sanborn offers a modern instrument designed with *his* particular needs in mind: the 2-speed "office standard" *Model 100 Viso-Cardiette* . . . its mobile counterpart, the *Model 100M Mobile Viso-Cardiette* . . . and the 18-pound *Model 300 Visette. Only Sanborn* makes all three.

Descriptive Literature and Prices on request, from your Sanborn Branch Office, Service Agency or the Main Office.

SANBORN COMPANY

MEDICAL DIVISION, 175 Wyman St., Waltham 54, Massachusetts

2 reliable oral anticoagulants

Tromexan

ethyl biscoumacetate Geigy

"...of real value in acute anticoagulant therapy."[1]

- rapid, therapeutic hypoprothrombinemia within 18-24 hours[2,3]
- on discontinuance of therapy prothrombin time returns to normal with exceptional rapidity[4]
- well tolerated

Sintrom

acenocoumarol Geigy

smooth-acting anticoagulant of intermediate rate of action

- prompt, therapeutic hypoprothrombinemia within 36-48 hours[5-7]
- prolonged, stable effect evenly sustained with single, low, daily dose[5-7]
- ready reversal of action[5,8]
- well tolerated[5,6,8]

(1) Mayer, G. A., and Connell, W. F.: Canad. M.A.J. 77:930 (Nov. 15) 1957.
(2) Burke, G. E., and Wright, I. S.: Circulation 3:164, 1951.
(3) Vander Veer, J. B., Funk, E. H., Jr., Boyar, F. R., and Keller, E. A.: Am. J. Med. 14:694, 1953.
(4) Scarrone, I. A., Beck, D. F., and Wright, I. S.: Circulation 6:489, 1952.
(5) Neill, E. C., Moon, R. Y., and Vander Veer, J. B.: Circulation 15:713, 1957.
(6) Rulla, F. R., Bartels, C. C., and Evans, J. A.: J.A.M.A. 168:743 (Oct. 11) 1958.
(7) Menendez, C., Almonte, J. C., and Ramos, C. N.: Angiology 8:182, 1957.
(8) Mayer, G. A., and Connell, W. F.: Canad. M.A.J. 76:272 (Feb. 15) 1957.

Tromexan® (ethyl biscoumacetate Geigy). Scored tablets of 150 mg. and 300 mg.
Sintrom® (acenocoumarol Geigy). Double-scored tablets of 4 mg.

Geigy

Ardsley, New York
03059

for the tense and nervous patient

relief comes fast and comfortably

–does not produce autonomic side reactions
–does not impair mental efficiency, motor control, or normal behavior.

Usual Dosage: One or two 400 mg. tablets t.i.d.

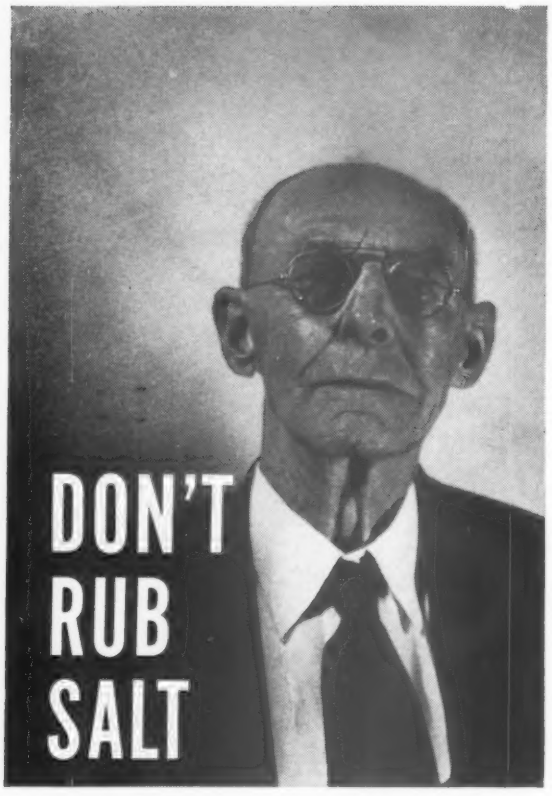
Supplied: 400 mg. scored tablets, 200 mg. sugar-coated tablets or as MEPROTABS*—400 mg. *unmarked,* coated tablets.

Miltown®

meprobamate (Wallace)

WALLACE LABORATORIES / *New Brunswick, N. J.*

CM-8284



IN HIS CARDIAC WOUND

Modern saluretics may *seem* to have made unlimited salt intake possible for cardiac and hypertensive patients. Yet despite the improvements in diuretic therapy, sodium restriction is still important in the prophylaxis of edema. The wise physician does not add needlessly to the burden of his patient, nor test unnecessarily the power of the drugs he prescribes. It makes good sense to him to prescribe DIASAL —which looks, tastes and flavors food exactly like salt . . . but is sodium free.

Diasal contains potassium chloride, glutamic acid and inert ingredients. Supplied in shakers and 8 oz. bottles.

prescribe **DIASAL**®

sodium-free salt substitute

FOUGERA

E. Fougera & Co., Inc. • Hicksville, New York

for the cardiac/ hypertensive obese

NEW! TENUATE

(diethylpropion)

hunger control free of pressor effects

New Tenuate produces a pure anorexic effect, free of CNS stimulation.[1] EKG studies[2] prove Tenuate does not affect heart rate, blood pressure, pulse or respiration.

Tenuate produces a satisfactory, progressive weight loss, often with minimum reliance on strict dieting or calorie counting.[1]

Dosage: *One 25 mg. tablet one hour before meals. To control nighttime hunger, an additional Tenuate tablet in mid-evening will not induce insomnia.*

hunger control for any obese patient

1. Spielman, A.D.: Mich. Acad. Gen. Prac. Symposium, Detroit, 1959.
2. Alfaro, R. D. and Gracanin, V.: *to be published.*

TRADEMARK: 'TENUATE'

Merrell

THE WM. S. MERRELL COMPANY

NEW YORK • CINCINNATI • ST. THOMAS, ONTARIO

A quinidine of choice in atrial fibrillation, flutter, premature contractions, auricular tachycardia.

DOSAGE: see PDR for dosage, etc.

SUPPLIED: Bottles of 30, 100, 250.

1. Bellet, S.; Finkelstein, D., and Gilmore, H.: A.M.A. Archives Int. Med. 100:750, 1957.
2. Bellet, S.: Amer. Heart J. 56:479, 1958.
3. Finkelstein, D.: Penn. Med. J. 61:1216, 1958.

REFER TO PDR PAGE 893

for samples and literature, write . . .

WYNN PHARMACAL CORPORATION

5119 West Stiles Street, Philadelphia 31, Pa.

also available:
INJECTABLE QUINAGLUTE
10 cc. Multiple Dose Vials, 0.08 Gm. Quinidine Gluconate per cc.

***U. S. Patent 2895881**

no longer need patients be denied quinidine benefits in cardiac arrhythmias because of g.i. distress

QUINAGLUTE™ DURA-TAB® S.M.

provides **well tolerated quinidine gluconate** (ten times as soluble as quinidine sulfate) in Sustained Medication* form

oral b.i.d. dosage
(every 12 hours)
Each Quinaglute Dura-Tab S.M. dose maintains uniform effective plasma levels up to 12 hours. Night dosage unnecessary. Safer, more efficient — no valleys where arrhythmias tend to recur.[1-3]

Before Esidrix:
Weight 176 lbs.

27 pounds lost in 19 days; ascites and pedal edema reduced with

Esidrix[T.M.]
(hydrochlorothiazide CIBA)

pre-eminently effective whenever diuresis is desired
Indicated in: congestive heart failure ■ nephrosis and nephritis ■ toxemia of pregnancy ■ premenstrual edema ■ edema of pregnancy ■ steroid-induced edema ■ edema of obesity.

After 19 Days on Esidrix:
Weight 149 lbs.

H. K., 44 years old, with history of heavy drinking. Previously hospitalized in 1954, with diagnosis of Laennec's cirrhosis. Admitted on 3/3/59, patient complained of swollen abdomen, swelling in both legs and exertional dyspnea.

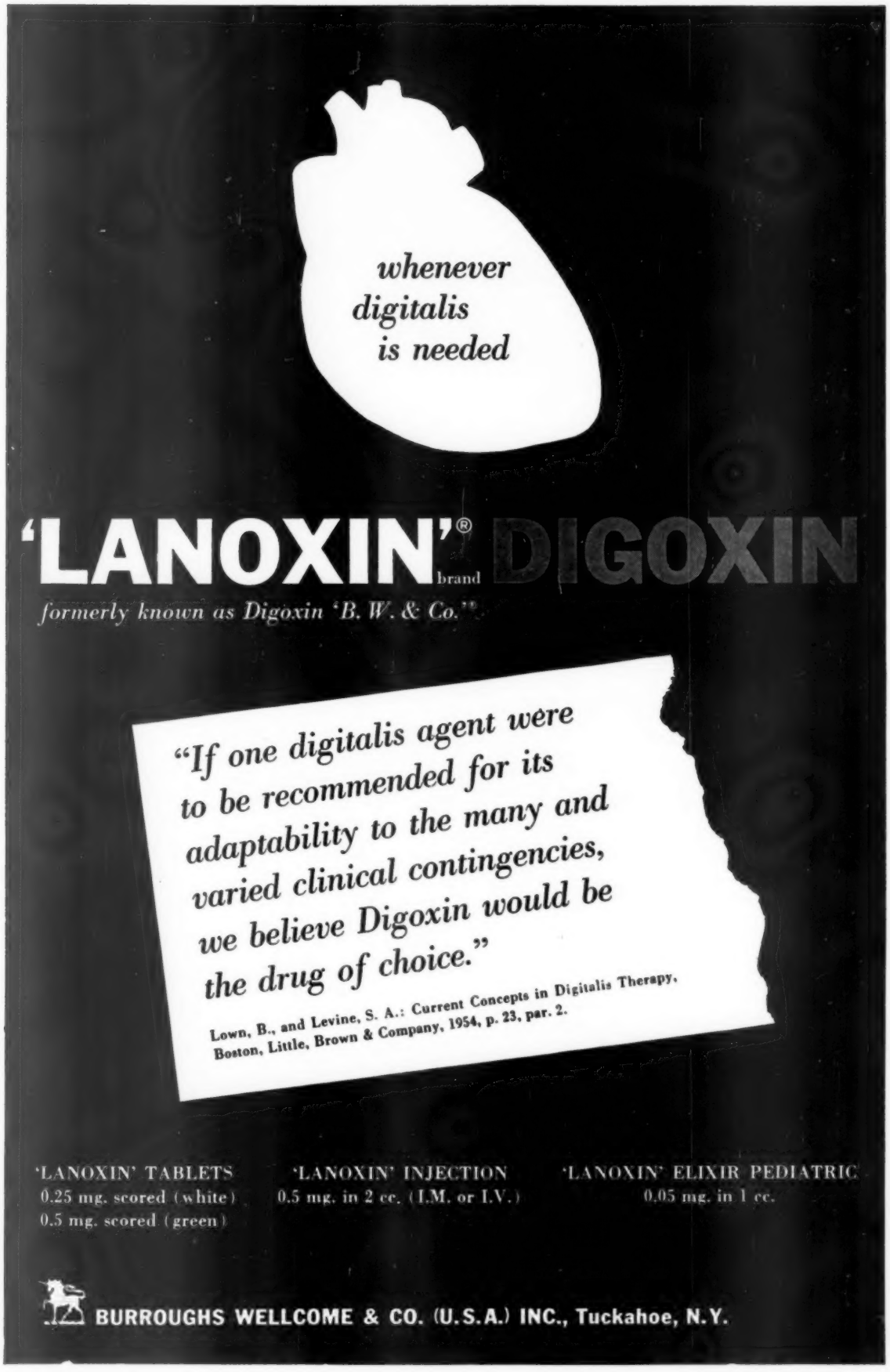
Findings: Abdomen enlarged in girth with definite fluid wave; liver palpated 4 fingerbreadths below the costal margin; pedal edema (4+). Patient not in acute distress. Blood pressure, 140/80 mm. Hg; pulse, 112/min.; respiration, 20/min.

Treatment: Mercurial diuretic on 3/3 and 3/4, followed by Esidrix, 50 mg. b.i.d., from 3/5 to 3/23 when patient signed out of hospital. Esidrix induced copious diuresis resulting in almost complete disappearance of edema.

Supplied: Esidrix *Tablets,* 25 mg. (pink, scored) and 50 mg. (yellow, scored); bottles of 100 and 1000.

CIBA
SUMMIT, N. J.

2/2713MK


whenever
digitalis
is needed
'LANOXIN'® brand DIGOXIN
formerly known as Digoxin 'B. W. & Co.'
"If one digitalis agent were to be recommended for its adaptability to the many and varied clinical contingencies, we believe Digoxin would be the drug of choice."
Lown, B., and Levine, S. A.: Current Concepts in Digitalis Therapy, Boston, Little, Brown & Company, 1954, p. 23, par. 2.
'LANOXIN' TABLETS
0.25 mg. scored (white)
0.5 mg. scored (green)
'LANOXIN' INJECTION
0.5 mg. in 2 cc. (I.M. or I.V.)
'LANOXIN' ELIXIR PEDIATRIC
0.05 mg. in 1 cc.
BURROUGHS WELLCOME & CO. (U.S.A.) INC., Tuckahoe, N.Y.

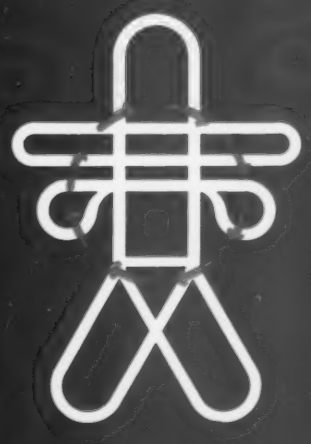
DISSOLVES INTRAVASCULAR

NOT JUST A NEW DRUG...*A NEW THERAPY*

ACTASE

TRADEMARK

Fibrinolysin (Human)



1. Moser, K.M.: J.A.M.A. *167*:1695 (Aug. 2) 1958.
2. Cliffton, E.E.: J. Am. Geriatrics Soc. *6*:118, 1958.
3. Sussman, B.J., and Fitch, T.S.P.: J.A.M.A. *167*:1705 (Aug. 2) 1958.
4. Singher, H.O., and Chapple, R.V.: Clin. Med. *6*:439 (March) 1959.

ORTHO PHARMACEUTICAL CORPORATION, RARITAN, N. J.

AR CLOTS

in thrombophlebitis and pulmonary embolism

Clinically proved,[1-3] ACTASE has a specific lytic effect upon the venous thrombus or pulmonary embolus. Patients respond rapidly, often dramatically, to the clot-dissolving action of an intravenous infusion of this physiologic fibrinolysin.[4] A significant decrease in length of hospitalization following thrombophlebitis, as well as a reduction in the threat of pulmonary embolism, is now possible. In one series of patients with deep thrombophlebitis, some of whom had previously suffered pulmonary emboli, no occurrence of pulmonary emboli was reported following administration of ACTASE[1]

Ortho

COMPLETE INFORMATION AVAILABLE ON REQUEST.

Index to Advertisers

January, 1960

American Cystoscope Makers, Inc. 36
Amfre-Grant, Inc. 27
Armour Pharmaceutical Company 8

Beck-Lee Corporation 1
Burroughs Wellcome & Co. Inc. 38, 55

Cereal Institute, Inc. 40
Ciba Pharmaceutical Products, Inc. 10, 26, 39, 54

Davol Rubber Company 28, 29

The Evron Company, Inc. 4

E. Fougera & Co., Inc. 52

Geigy Company 25, 50

Ives-Cameron Company 19, 20, 21, 22

Thos. Leeming & Co., Inc.. . . . . *Inside Back Cover*
Eli Lilly and Company 32

Merck Sharp & Dohme, Division of Merck & Co., Inc. 42, 43
The Wm. S. Merrell Company 52

Ortho Pharmaceutical Corporation 56, 57

Pfizer Laboratories, Division, Chas. Pfizer & Co., Inc. 31, 41

Riker Laboratories, Inc. . . . . *Back Cover*
Roche Laboratories, Div. of Hoffmann-LaRoche, Inc. 6
J. B. Roerig Co., Division, Chas. Pfizer & Co., Inc. 14

Sanborn Company 49
G. D. Searle & Co. 45, 46, 47, 48
Smith Kline & French Laboratories 18
E. R. Squibb & Sons, Division of Mathieson Chemical Corp. 30, 34

Charles C Thomas, Publisher 15

United States Catheter & Instrument Corp. 24

Walker Laboratories, Inc. 2
Wallace Laboratories 23, 33, 35, 51
Warner-Chilcott Laboratories 37
White Laboratories, Inc. 16, 17
Wyeth Laboratories . . . . . *Inside Front Cover*, 12, 13
Wynn Pharmacal Corporation 53

Clarin* can do this for your postcoronary patients

WITHOUT CLARIN, **turbid blood serum five hours after a fat meal:** This unretouched dark-field photomicrograph (2500X) shows potentially hazardous fat concentrations circulating in the blood stream of a patient after a standard fat meal.

WITH CLARIN, **clear blood serum five hours after a fat meal:** After eating a standard fat meal as at left, the same patient has taken one sublingual Clarin tablet. Note marked clearing effect and reduction in massive fat concentrations in this unretouched photomicrograph (2500X).

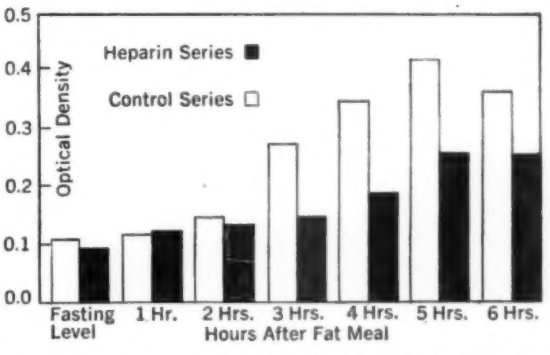
CLARIN is sublingual heparin potassium. One mint-flavored tablet taken after each meal effectively "causes a marked clarification of postprandial lipemic serum."[1] Clarin facilitates the normal physiologic breakdown of fats, with no effects on the blood-clotting mechanism.[1] It therefore provides important benefits for your postcoronary patients.

Indication: For the management of hyperlipemia associated with atherosclerosis.

Dosage: After each meal, hold one tablet under the tongue until dissolved.

Supplied: In bottles of 50 pink, sublingual tablets, each containing 1500 I.U. heparin potassium.

1. Fuller, H. L.: Angiology 9:311 (Oct.) 1958.
2. Shaftel, H. E., and Selman, D.: Angiology *10*:131 (June) 1959.



Average serum optical density in 36 patients after fat meal with and without sublingual heparin.[2]

*Registered trade mark. Patent applied for.

Thos. Leeming & Co., Inc. New York 17, N. Y.